RUTGERS
Cancer Institute
of New Jersey

Immunotherapy for the Treatment of GU Malignancies

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Disclosures

- None

Disclosures

Learning Objectives

- Discuss current treatment strategies for kidney cancer, prostate cancer, and bladder cancer
- Review the role of immunotherapy in the management of genitourinary malignancies
- Discuss selected immunotherapy clinical trials at CINJ

Principles of Immunotherapy

- Based on immune system's ability to recognize and destroy cancer cells
  - Potential for long-term results (durable responses)
  - Lack of typical drug resistance
  - Auto-immune toxicities (different from conventional drugs)

- Effective tumor immunotherapy treatments are designed to:
  - Promote cancer-immunity cycle
  - Block immune suppression of tumors

Kaufman HL. JCO 2015;33:1-3.

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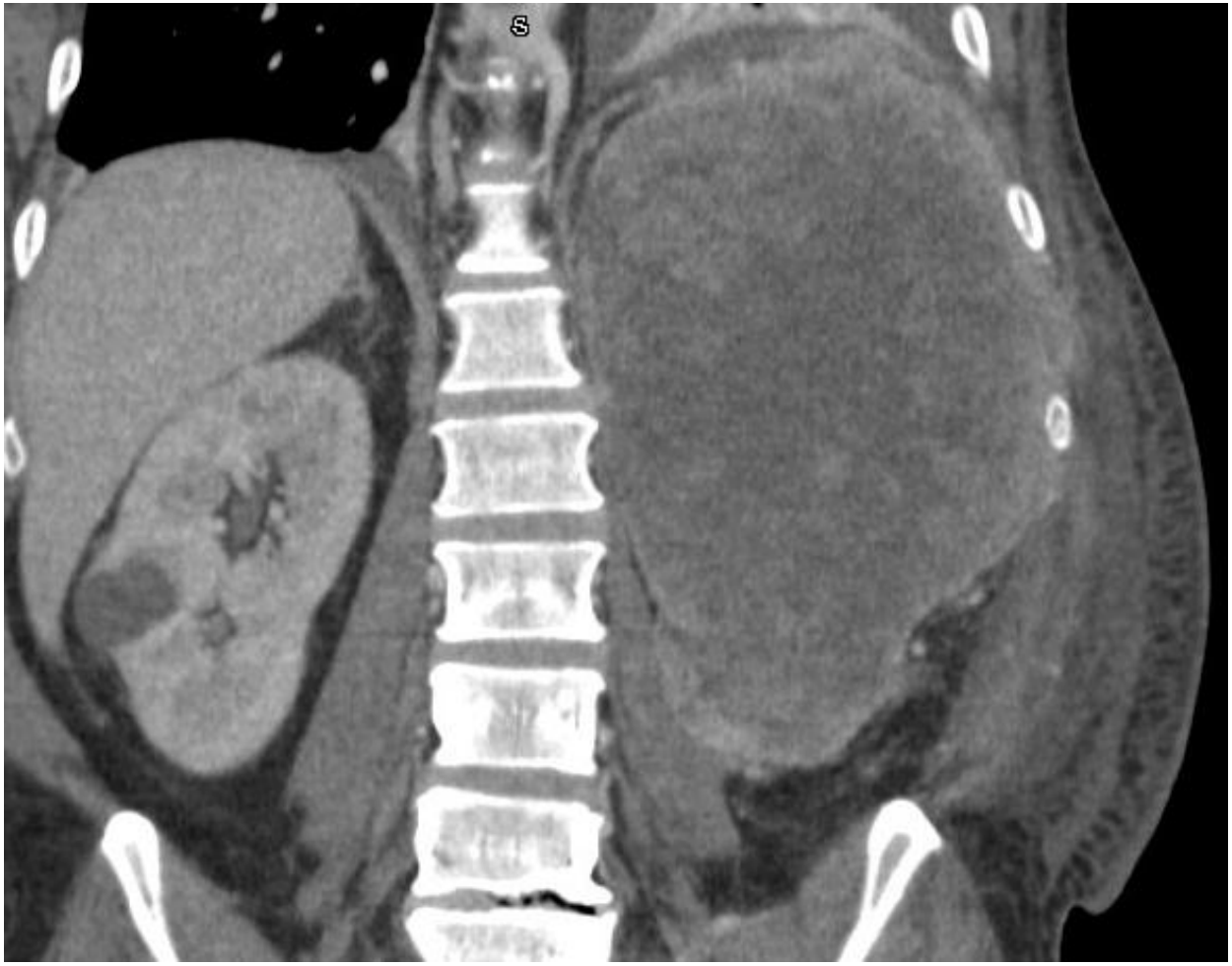
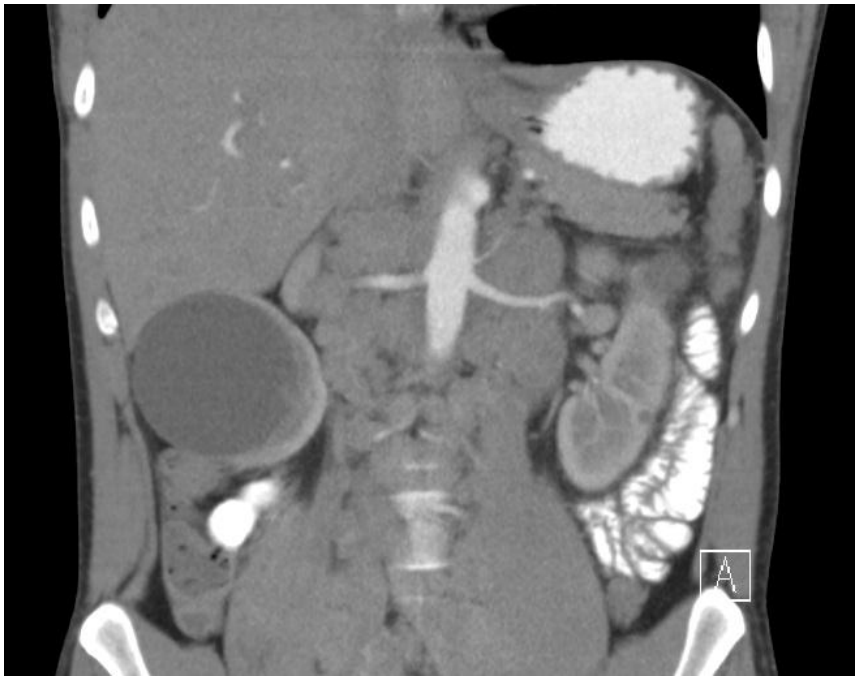
Renal Cell Carcinoma

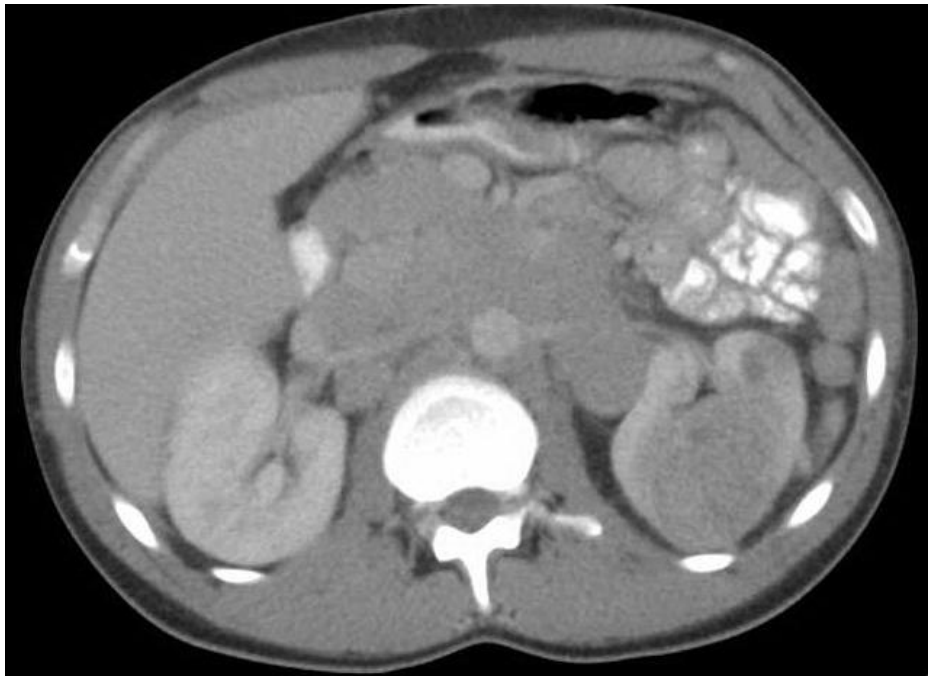
Advanced RCC



53 y.o. man with a 20x20cm kidney tumor.

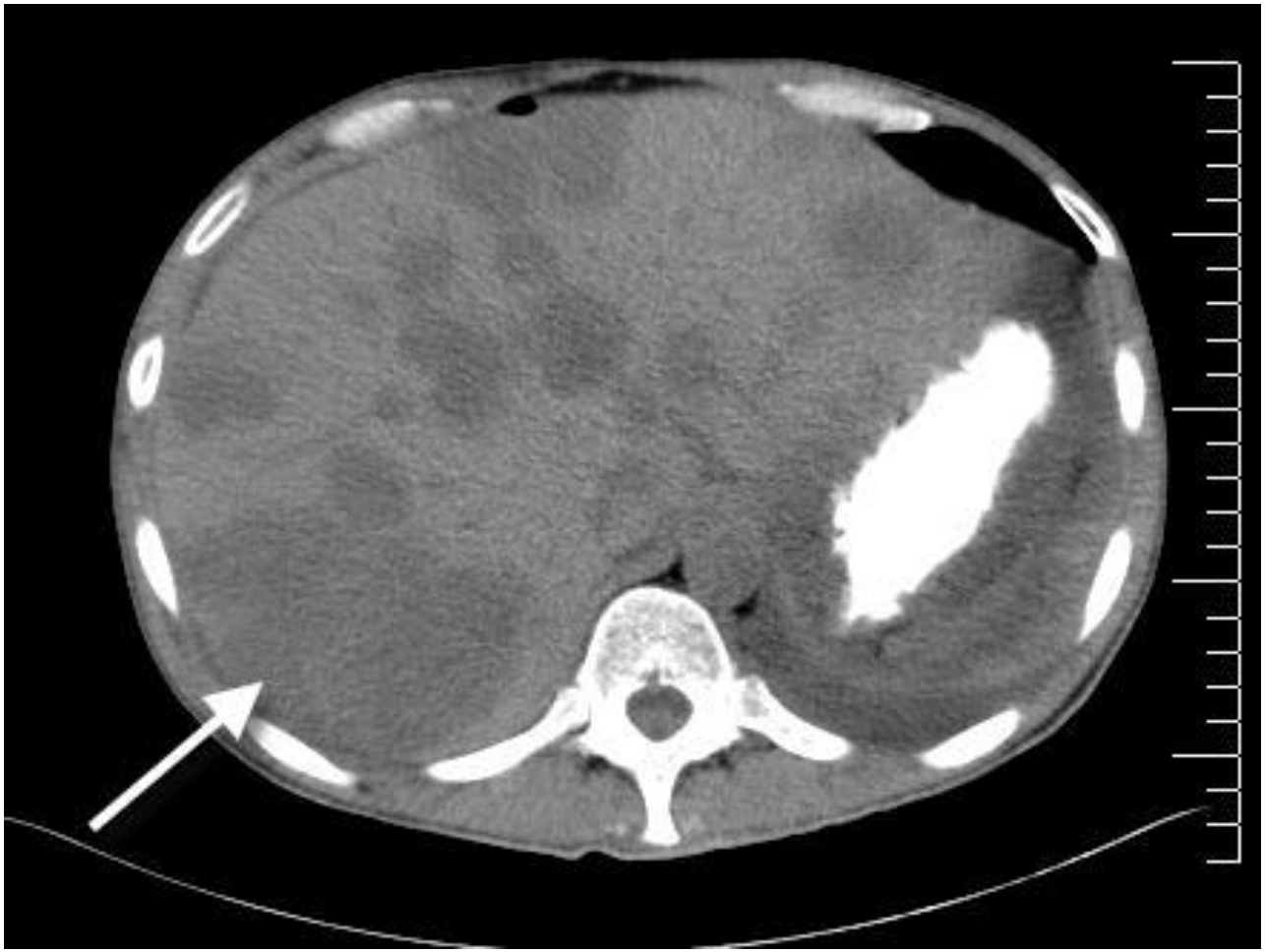
Advanced RCC





24 y.o. man with bulky retroperitoneal lymphadenopathy

Advanced RCC



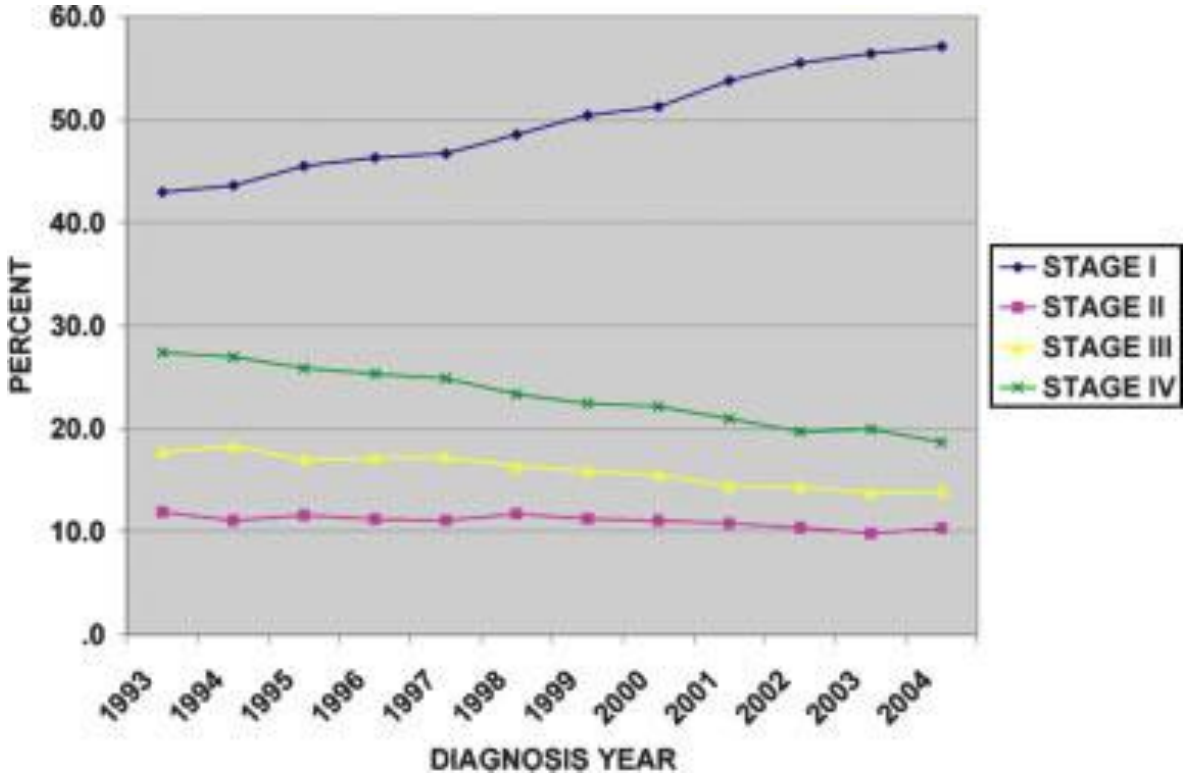
56 y.o. woman with extensive liver mets

Burden of Kidney Cancer

- Approximately 61,560 new cases diagnosed and an estimated 14,080 deaths in U.S. in 2015 (Siegel et al. *CA Can J Clin* 2015)
  - 7th and 10th most common malignancy in men and women, respectively
- Americans face a diagnosis of renal malignancy at a rate of approximately 1 in 67 over the course of their lifetime (Altekruse et al. *SEER* 2009)

Burden of Kidney Cancer

National Cancer Database

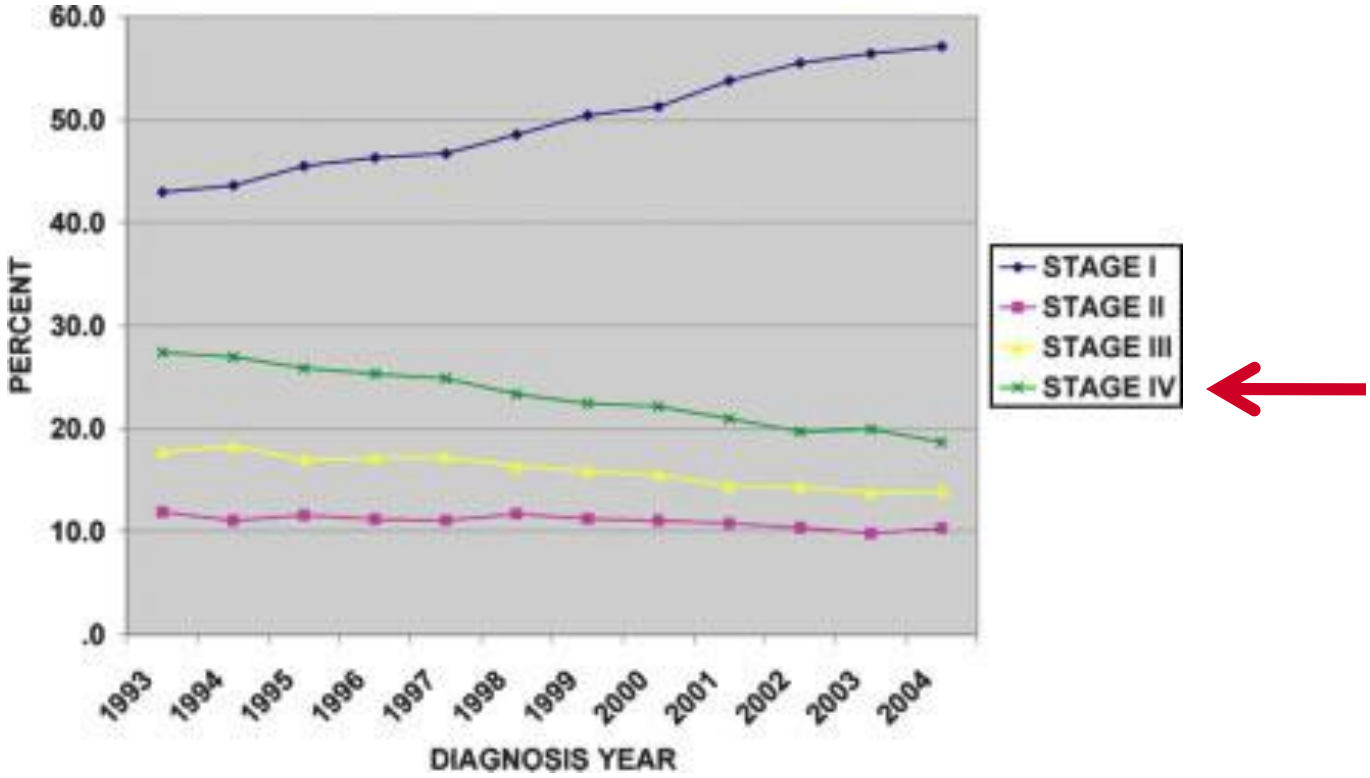


RCC stage distribution by diagnosis year

Kane et al. *Cancer* 2008

Burden of Kidney Cancer

National Cancer Database



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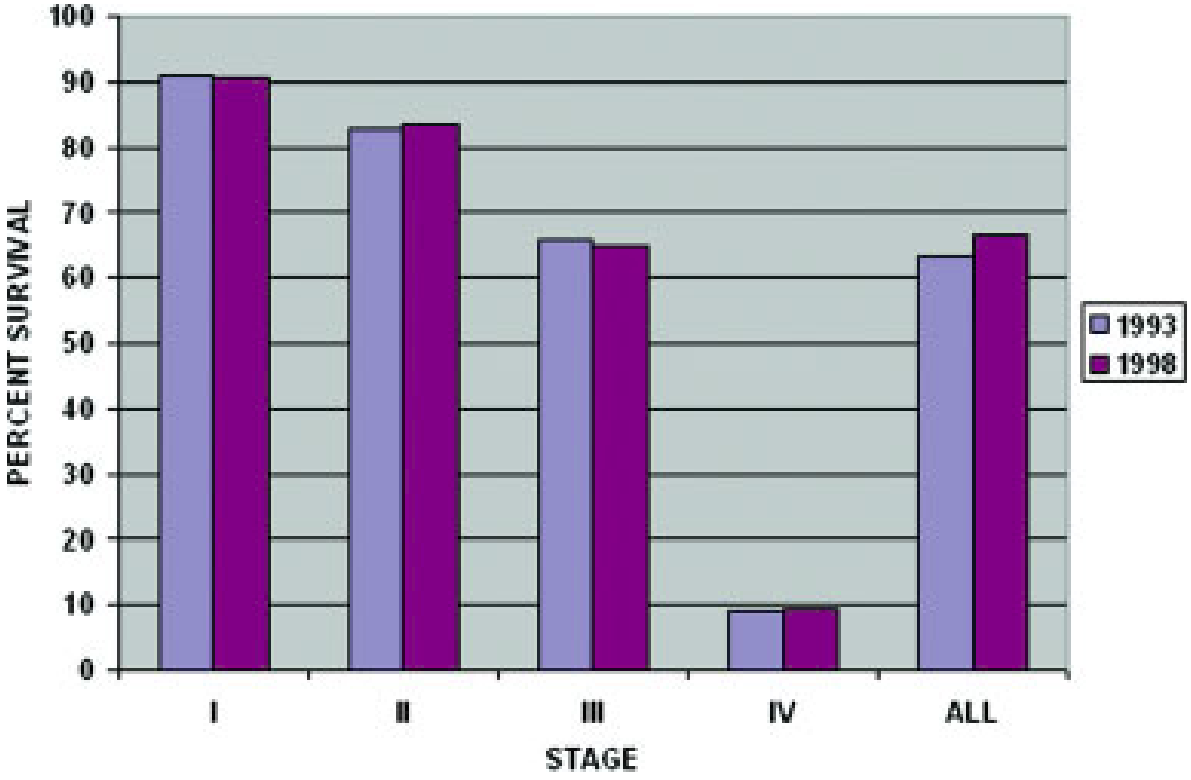
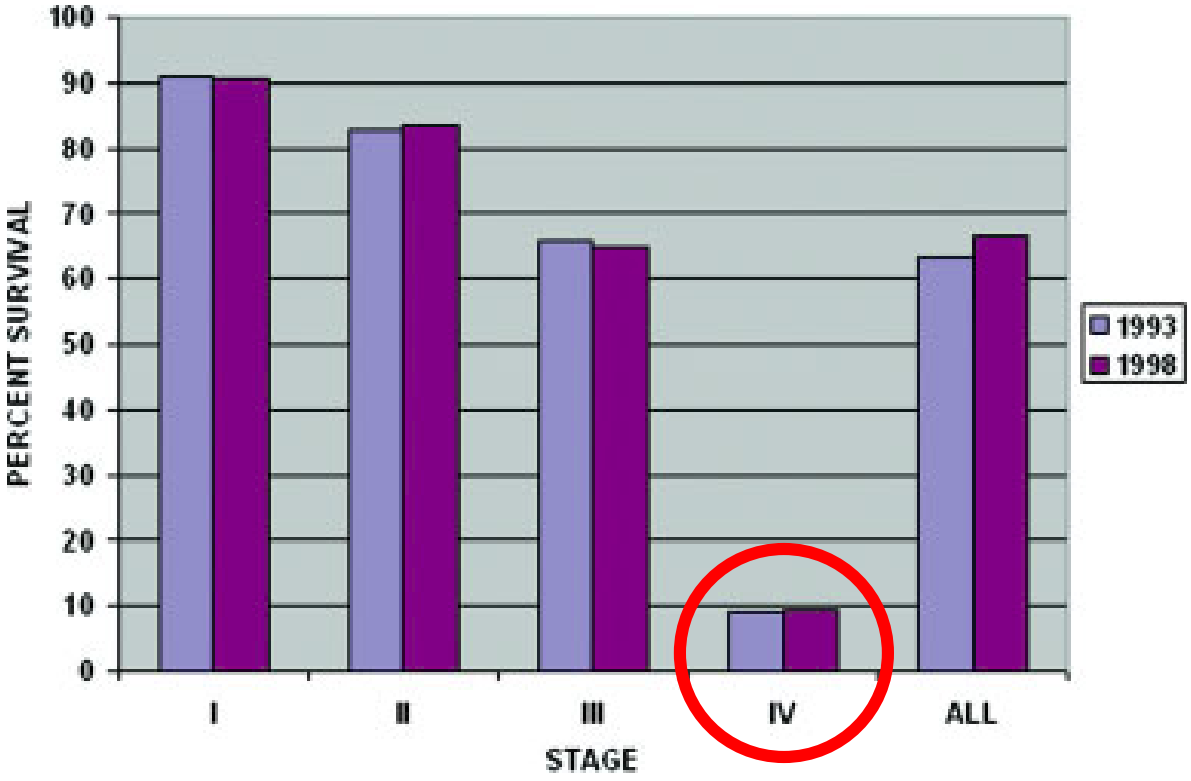


RCC 5-year survival by AJCC stage

Kane et al. *Cancer* 2008

Burden of Kidney Cancer

National Cancer Database



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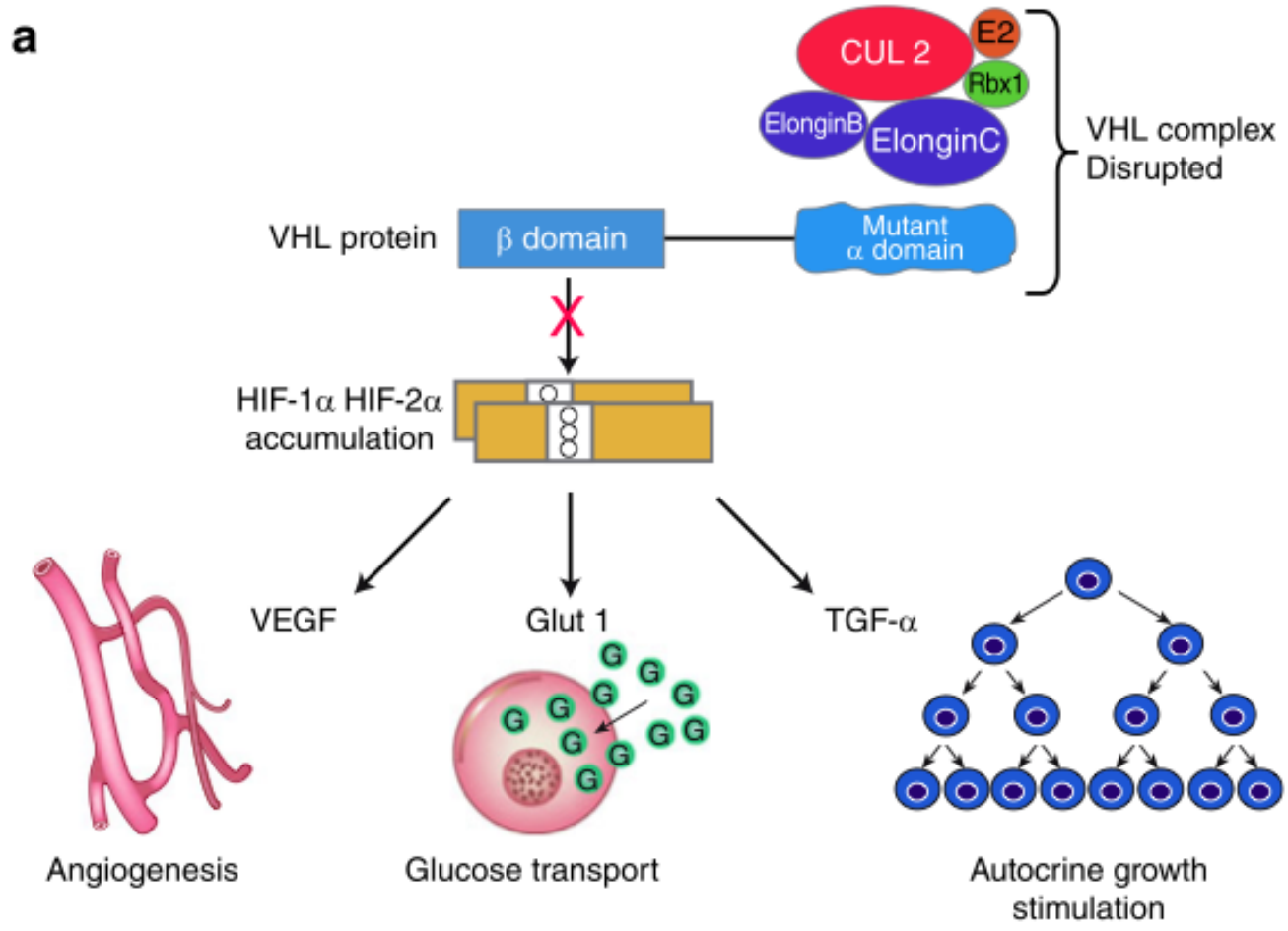
Kane et al. *Cancer* 2008

VHL Gene Complex



Singer et al. Curr Urol Rep 2011

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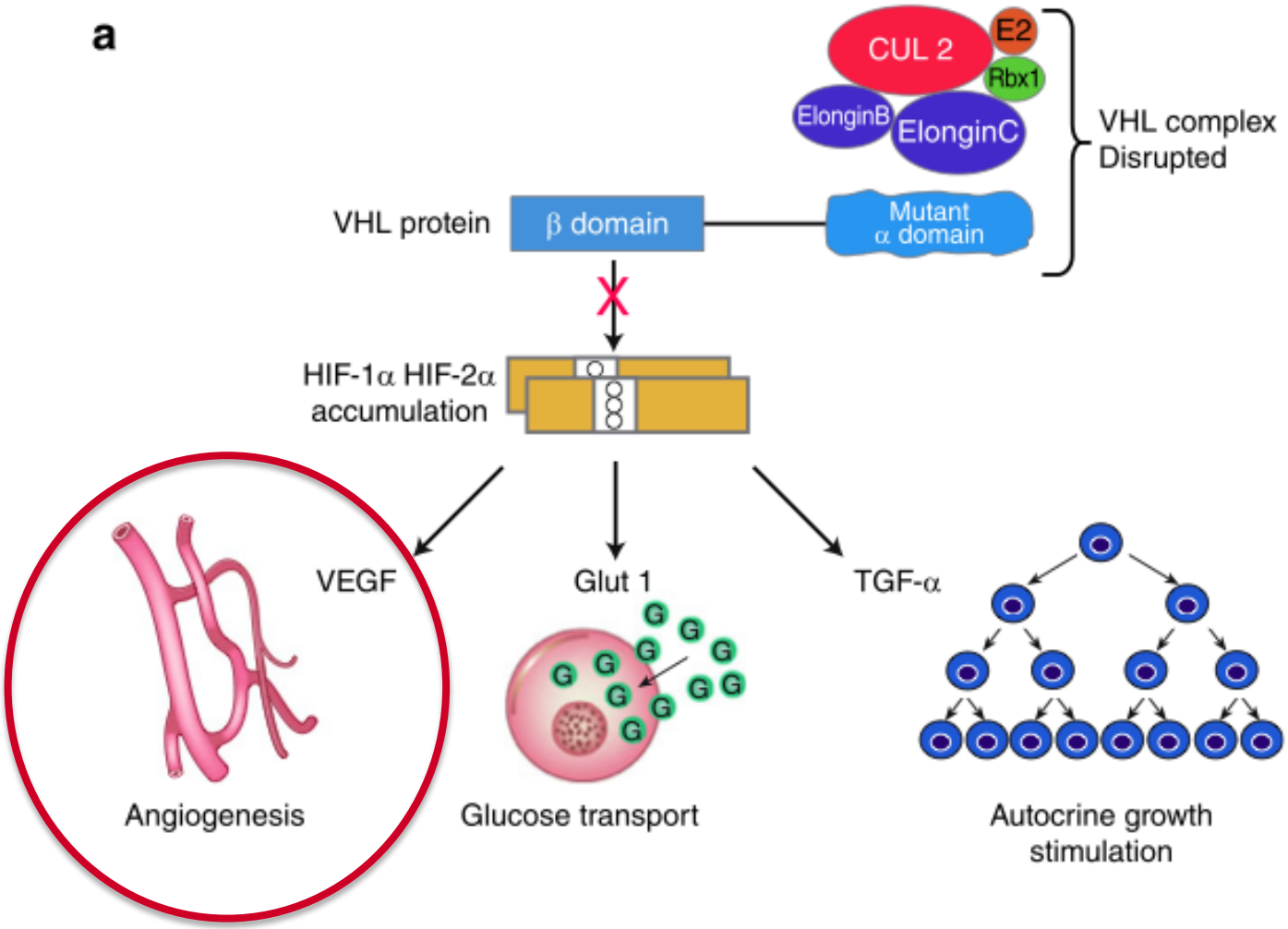

Singer et al. Curr Urol Rep 2011

Targeted Therapies for Kidney Cancer

Table 2. Key phase 3 trials of FDA-approved targeted therapies for advanced renal cell carcinoma

Therapy	Target	Treatment line	Comparison arm	Primary endpoint
Sunitinib [5]	VEGFR	Firstline	IFN-α	PFS
Temsirolimus [6]	mTOR	Firstline	IFN-α	OS
Bevacizumab + IFN-α (AVOREN) [7]	VEGF	Firstline	Placebo + IFN-α	OS
Bevacizumab + IFN-α (CALGB) [8]	VEGF	Firstline	IFN-α	OS
Sorafenib [9]	VEGFR	Cytokine failure	Placebo	OS
Everolimus [10]	mTOR	VEGFR failure	Placebo	PFS
Pazopanib [11]	VEGFR	Firstline or cytokine failure	Placebo	PFS
Axitinib [12]	VEGFR	Secondline	Sorafenib	PFS

IFN, interferon; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Modified from [13].

Singer et al. Curr Opin Oncol 2013

Targeted Therapies for Kidney Cancer

Evolving therapeutic targets in renal cell carcinoma Singer *et al.*

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5 drugs targeting VEGF/VEGFR
2 drugs targeting mTOR

Singer et al. Curr Opin Oncol 2013

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Bevacizumab = monoclonal antibody against VEGF

Singer et al. Curr Opin Oncol 2013

Impact of TKIs on IL-2 Utilization for mRCC

- High-dose IL-2 is a highly morbid but potentially curative treatment for carefully selected patients with metastatic renal cell carcinoma (mRCC)

- Targeted therapies (TT) have revolutionized the treatment of mRCC in the past decade and have largely replaced immunotherapy such as high-dose interleukin-2 (HD IL-2)

- We evaluated trends in HD IL-2 use for mRCC in the TT era

Allard CB, et al. JCO 2015;33(suppl 7S):449

Impact of TKIs on IL-2 Utilization for mRCC

- Weighted sample representing an estimate of patients undergoing HD IL-2 treatment for mRCC from 2004 to 2012
  - Premier Hospital Database, a nationally representative hospital discharge database

- Assessed temporal trends in patient, disease, and hospital characteristics stratifying by era
  - Pre-TT uptake: 2004-2006; Uptake: 2007-2009; Post-uptake: 2010-2012
  - Fitted multivariable regression models, accounting for clustering and weighting, to identify predictors of HD IL-2 treatment toxicity and tolerability.

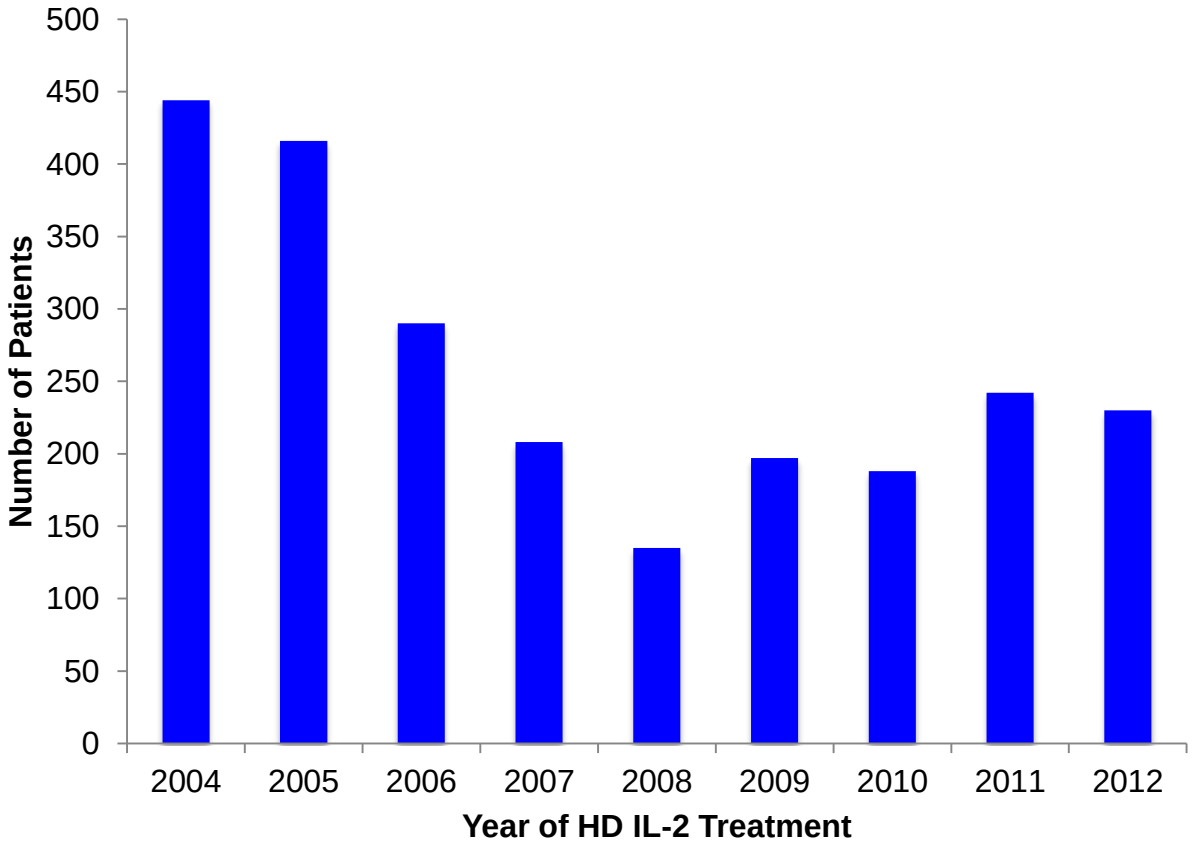
Allard CB, et al. JCO 2015;33(suppl 7S):449

Impact of TKIs on IL-2 Utilization for mRCC

- An estimated 2351 patients received HD IL-2 for mRCC in the United States from 2004 through 2012
- HD IL-2 use decreased from 2004 to 2008
- HD IL-2 became increasingly concentrated in academic centers, from 24% of treatments in 2004 to 89.5% in 2012
- Most HD IL-2 patients were men (75.3%), Caucasian (70.7%), aged <60 (59.6%), had lung metastases (60.9%), and were otherwise healthy (64.7% Charlson comorbidity index=0)

Allard CB, et al. JCO 2015;33(suppl 7S):449

High-Dose IL-2 Utilization for Kidney Cancer



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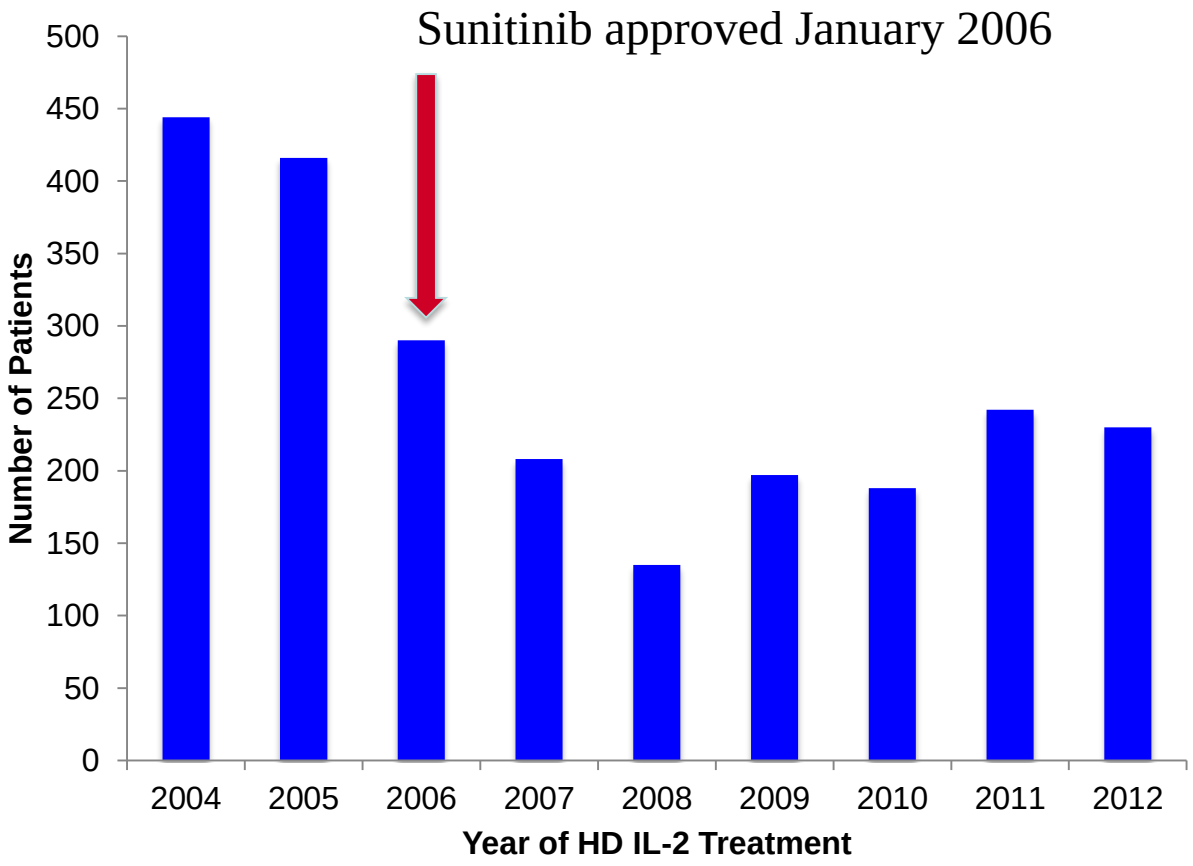
High-Dose IL-2 Utilization for Kidney Cancer



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Impact of TKIs on IL-2 Utilization for mRCC

- Toxicities were common, with 53.4%, 33.0%, and 7.1% requiring vasopressors, ICU admission, and hemodialysis respectively
- Factors associated with increased toxicities on multivariable analyses included being unmarried, male, and having multiple metastatic sites
- African Americans and patients with single metastatic sites were less likely to receive >1 treatment cycles

Allard CB, et al. JCO 2015;33(suppl 7S):449

Impact of TKIs on IL-2 Utilization for mRCC

- HD IL-2 is used infrequently for mRCC in the United States
- Patients selected for treatment are relatively young and healthy
- Despite strict patient selection, toxicities are common
- *HD IL-2 use has been increasingly restricted to academic centers since 2004, posing a possible barrier to patient access*

Allard CB, et al. JCO 2015;33(suppl 7S):449

Resurgence of Immunotherapy for RCC

- Rare CR with TT

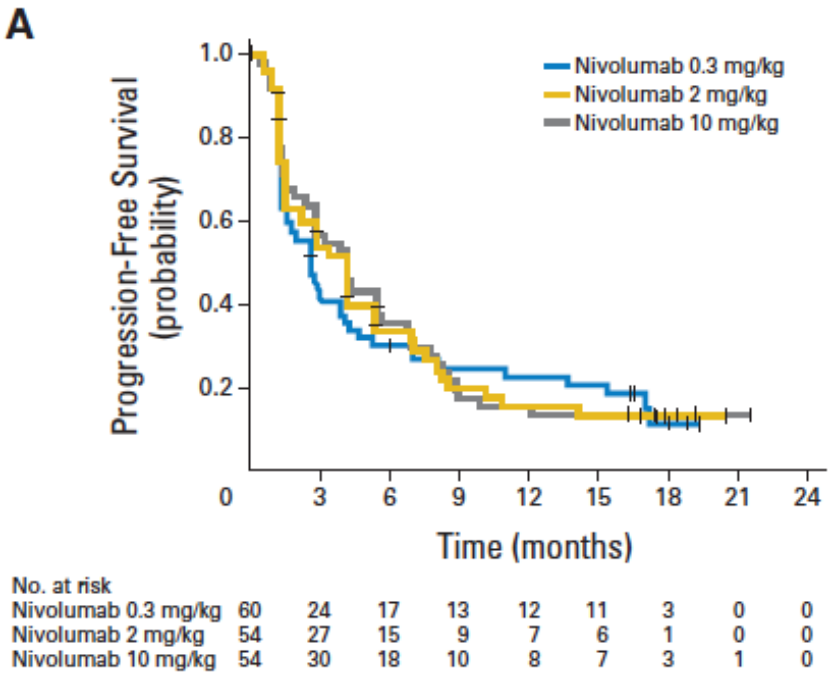
- Development of checkpoint inhibitors
  - Anti-PD-1 antibody that restores T-cell immune activity

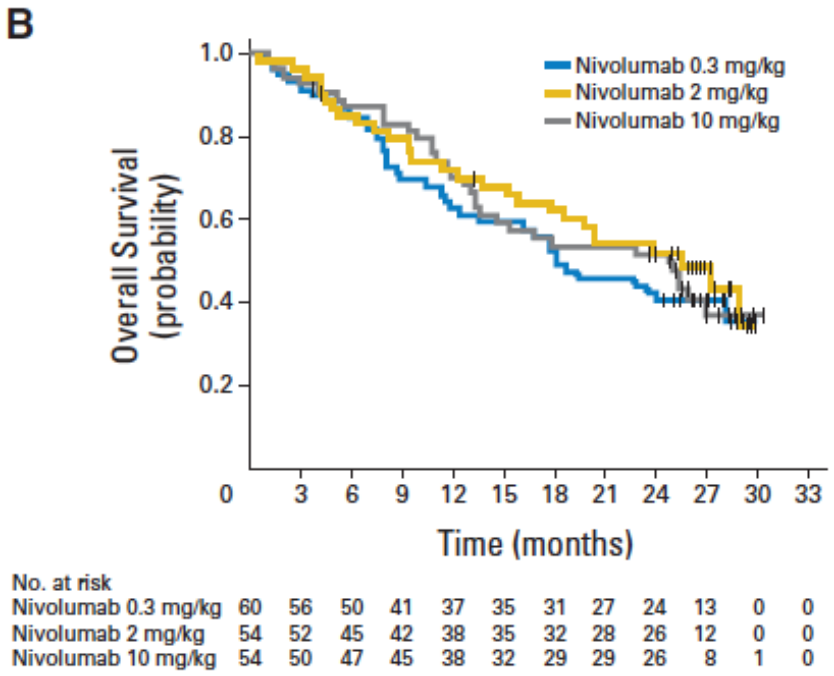
Nivolumab for Metastatic RCC: Results of a Randomized Phase II Trial

- 168 subjects with *previously treated clear cell mRCC*
  - VEGF/VEGFR
- Randomly assigned to nivolumab 0.3, 2, or 10 mg/Kg IV q3 weeks
  - PD-1 checkpoint inhibitor
- Endpoints:
  - Primary: evaluate dose-response relationship (PFS)
  - Secondary: objective response rate (ORR), overall survival (OS), and safety

Motzer et al. J Clin Oncol 2014

Nivolumab for Metastatic RCC: Results of a Randomized Phase II Trial





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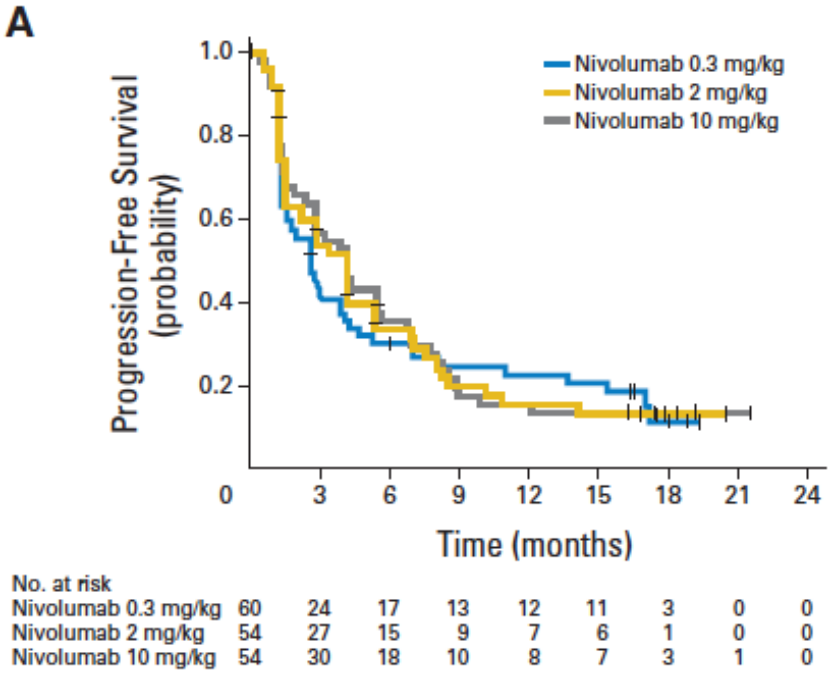

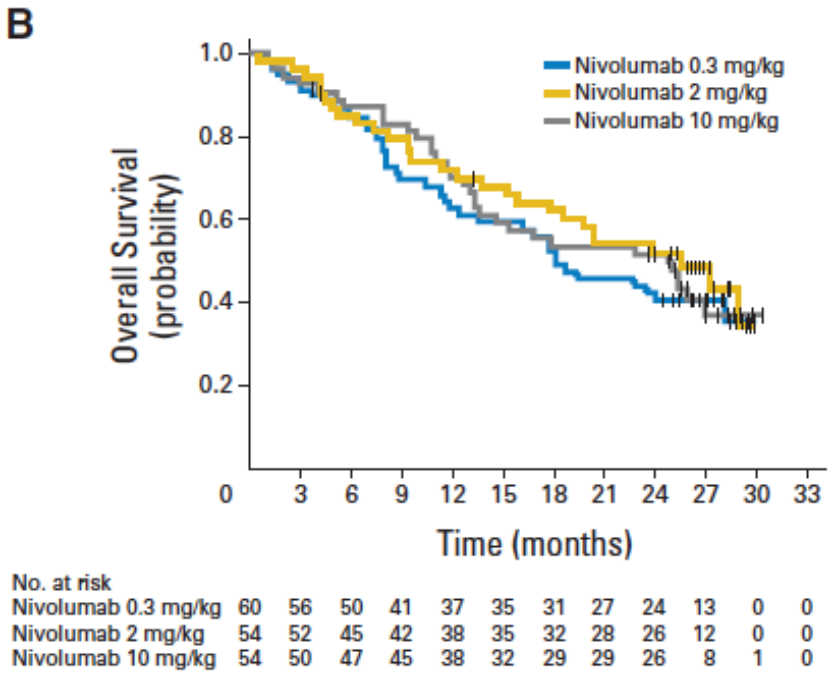

- **No dose-dependent relationship for PFS.**
- **Median PFS of 4.2 months (10mg/Kg)**

- **Median OS was 18.2 months, 25.5 months, and 24.7 months, respectively**
- **Greater than OS reported in pivotal phase III TT trials**

Motzer et al. J Clin Oncol 2014

Survival, Durable Response, Long-Term Safety in Patients with Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab

- 34 subjects with *previously treated advanced RCC*
  - At least 1 but not more than 5 prior systemic therapies
- Nivolumab 1 or 10 mg/Kg IV twice per week for up to 96 weeks
  - Subjects re-imaged after each 8 week treatment cycle up to 12 cycles
- Subjects received nivolumab until CR, unacceptable toxicty, or PD

McDermott et al. J Clin Oncol 2015

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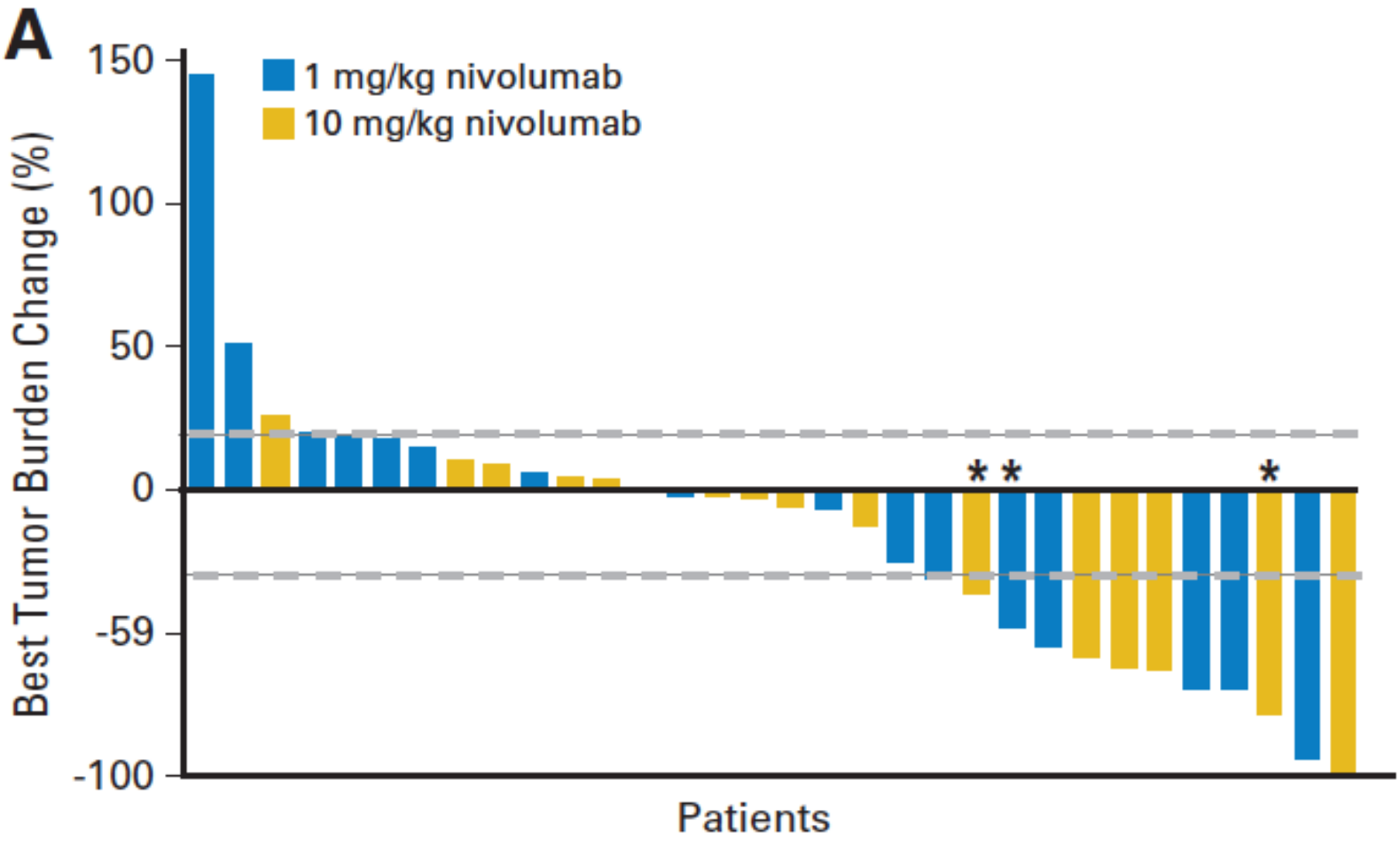

McDermott et al. J Clin Oncol 2015

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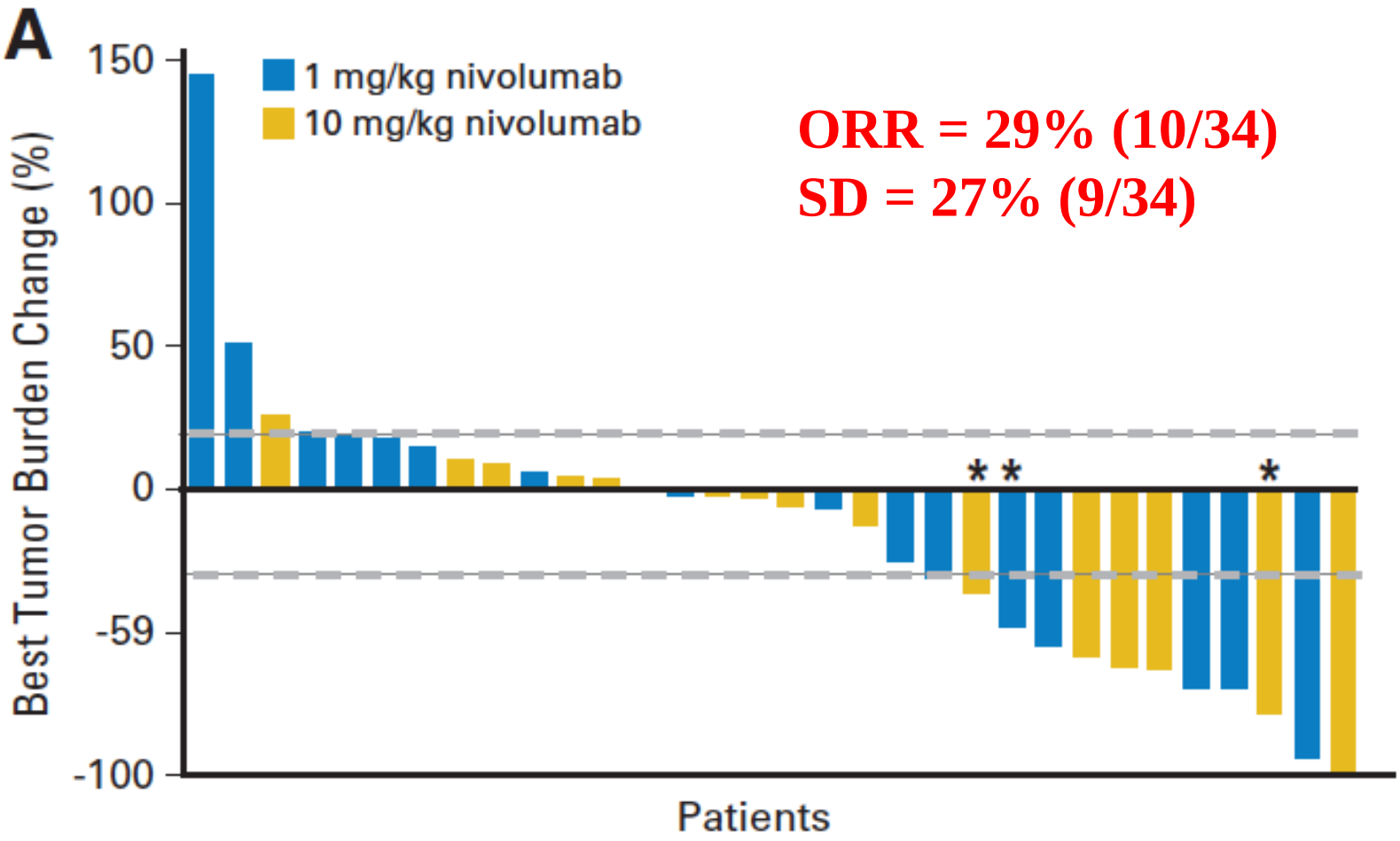

ORR = 29% (10/34)
SD = 27% (9/34)

McDermott et al. J Clin Oncol 2015

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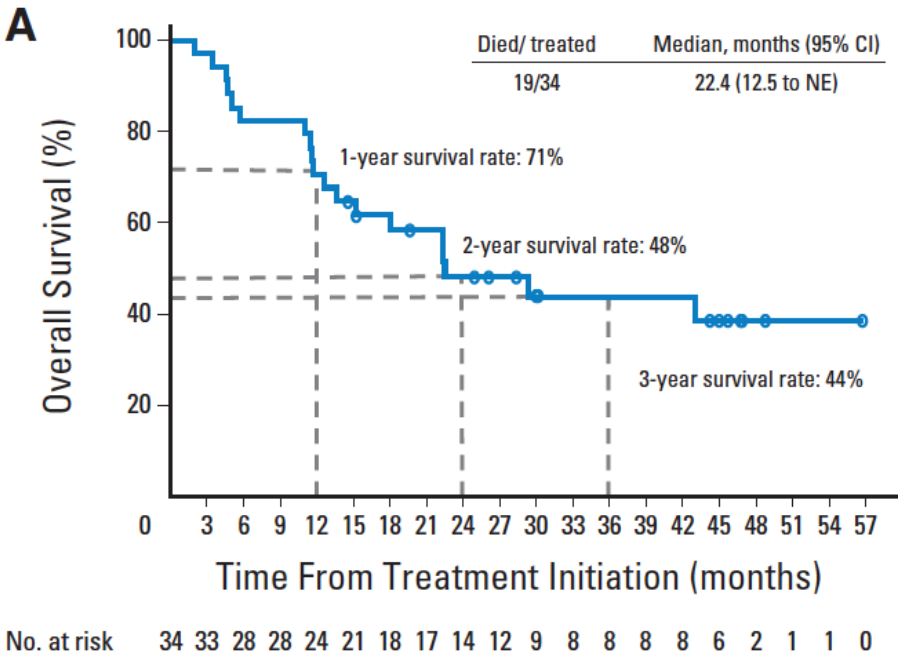

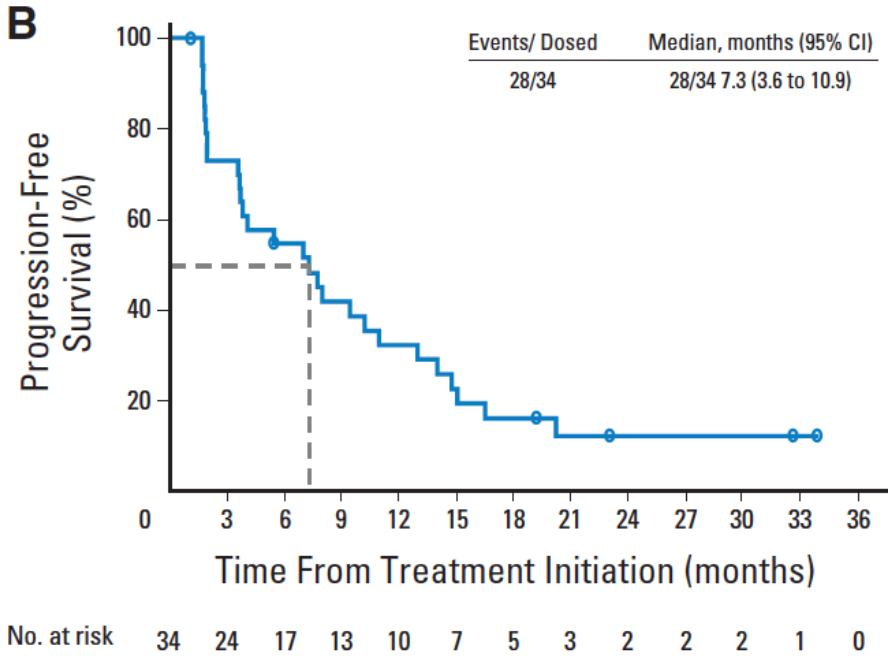

McDermott et al. J Clin Oncol 2015

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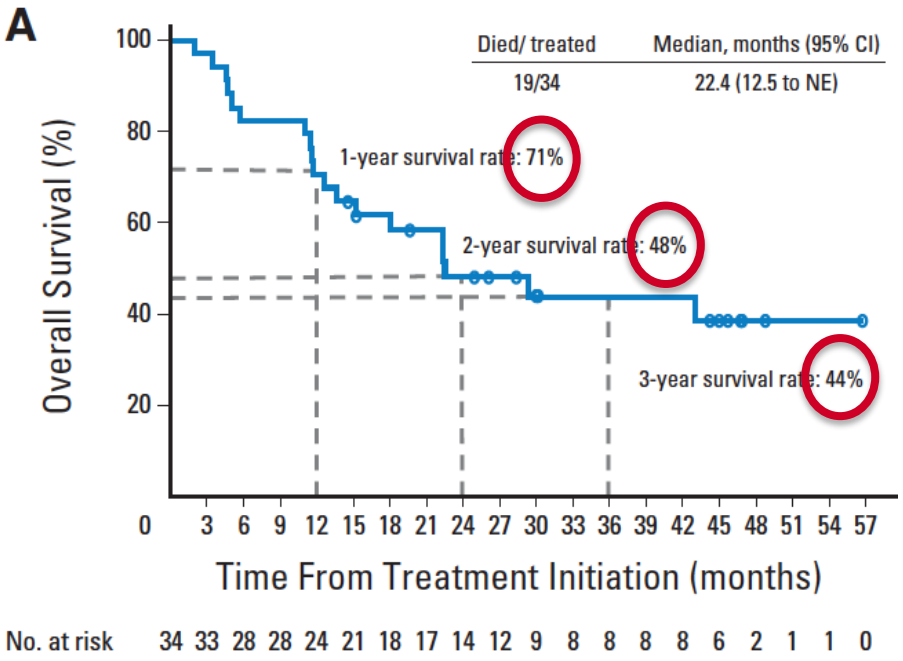
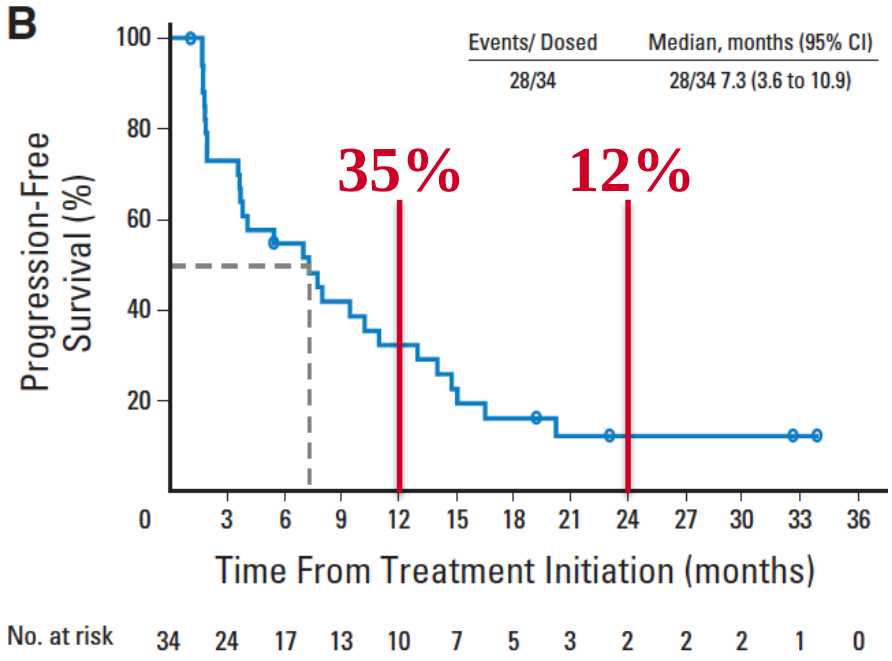




Median OS 22.4 months

Median PFS 7.3 months

McDermott et al. J Clin Oncol 2015

PD-1 Blockade Therapy in Renal Cell Carcinoma: Current Studies and Future Promises

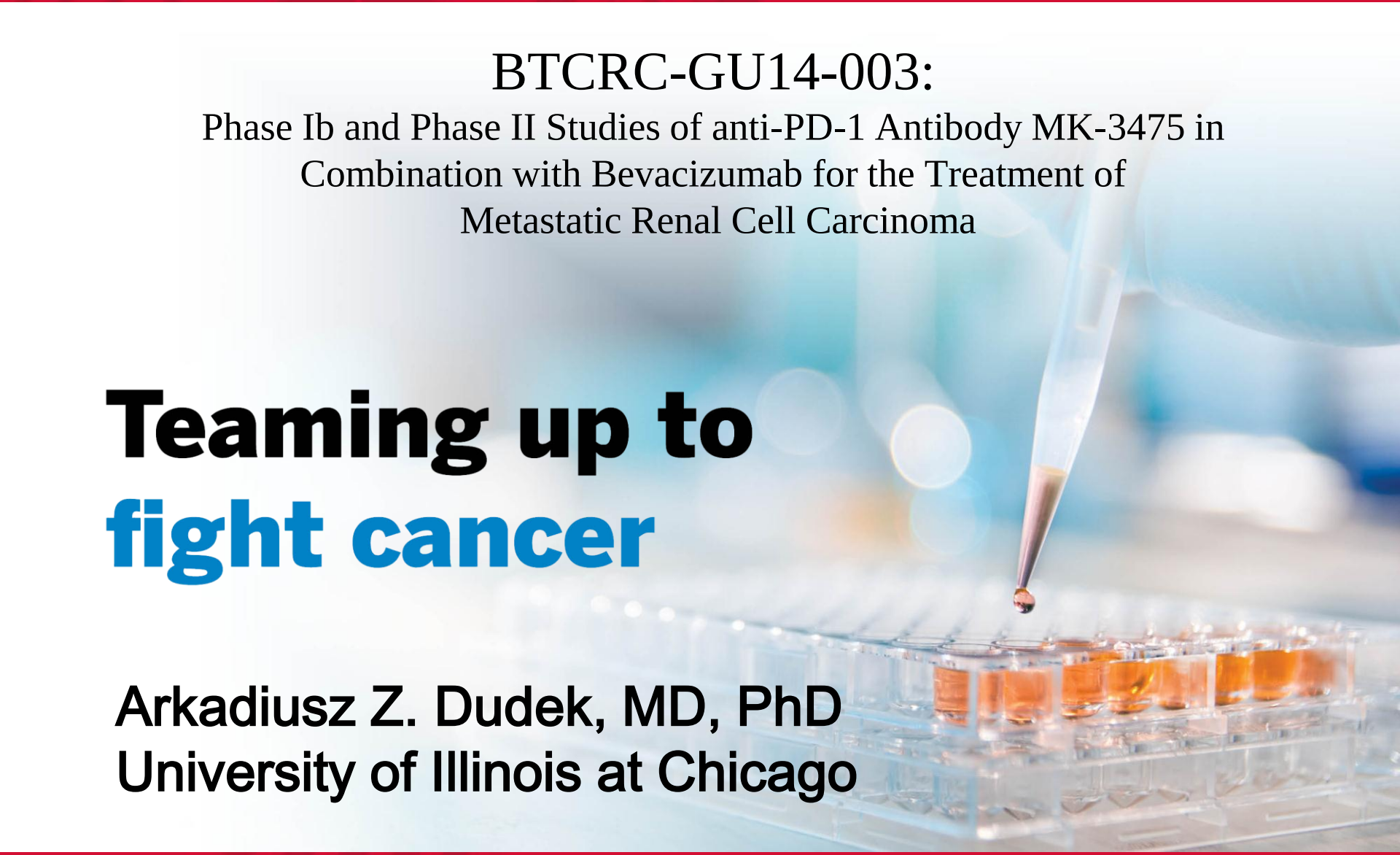
Table 3
Current trials focused on PD-1/PD-L1 blocking agents (www.clinicaltrials.gov). CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DC = dendritic cell; IDO1 = indoleamine 2,3-dioxygenase 1; IFN-α = interferon-α; LAG3 = lymphocyte-activation gene 3; RCC = metastatic renal cell carcinoma; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1.

Agents	Target	Trial ID number	Phase	Description
Nivolumab	PD-1	NCT01472081	I	In combination with ipilimumab at different doses in previously treated mRCC patients
		NCT01844505	III	vs. everolimus in mRCC patients who have received prior anti-angiogenic therapy
		NCT01358721	I	Characterization of peripheral immune cells, soluble factors, tumor immune infiltrates and markers in mRCC patients treated with nivolumab
		NCT02231749	III	In combination with ipilimumab vs. sunitinib in previously untreated mRCC patients
		NCT02210117	II	In combination with ipilimumab vs nivolumab plus bevacizumab as neoadjuvant therapy in mRCC patients eligible for cytoreductive nephrectomy
		NCT01968109	I	Anti-LAG-3 BMS-986016 With or without nivolumab in patients with advanced solid tumors including RCC
Pembrolizumab	PD-1	NCT02212730	I	Alone as neoadjuvant therapy in participants undergoing RCC tumor resection
		NCT02178722	I/II	in combination with the inhibitor of IDO1 INCB024360 in patients with advanced solid tumors including RCC
		NCT02014636	I/II	In combination with pazopanib in treatment naïve subjects with advanced RCC
		NCT02133742	I	In combination with axitinib in previously untreated mRCC patients
		NCT02089685	I/II	In combination with ipilimumab or IFN-α in patients with advanced melanoma or RCC
		NCT02179918	I	In combination with PF-05082566, a 4–1BB agonist monoclonal antibody in patients with solid tumors
Pidilizumab	PD-1	NCT01441765	II	Alone or in conjunction with DC/RCC fusion cell vaccine in mRCC patients
MPDL3280A	PD-L1	NCT01375842	I	Patients with advanced solid tumors including RCC
		NCT01984242	II	In combination with bevacizumab vs. sunitinib as first-line therapy in patients with mRCC
		NCT01988896	I	In combination with MEK inhibitor cobimetinib in patients with advanced solid tumors including RCC
		NCT02174172	I	In combination with ipilimumab or IFN-α in patients with advanced solid tumors including RCC
MEDI4736	PD-L1	NCT02118337	I	In combination with anti-PD-1 MEDI0680 in patients with advanced solid tumors including RCC
		NCT01975831	I	In combination with anti-CTLA-4 Tremelimumab in patients with advanced solid tumors including RCC

Massari et al. Cancer Treatment Reviews 2015;41:114-121.

BTCRC-GU14-003:

Phase Ib and Phase II Studies of anti-PD-1 Antibody MK-3475 in Combination with Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma



Arkadiusz Z. Dudek, MD, PhD
University of Illinois at Chicago

Member Institutions

- University of Illinois
- Indiana University
- University of Iowa
- University of Michigan
- Michigan State University
- University of Minnesota
- University of Nebraska
- Northwestern University
- Penn State University
- Purdue University
- ***Rutgers, The State University of New Jersey***
- University of Wisconsin

Background

- Tumor microenvironment may impact the efficacy of these immunotherapies and there is an interaction between immune response and tumor angiogenesis

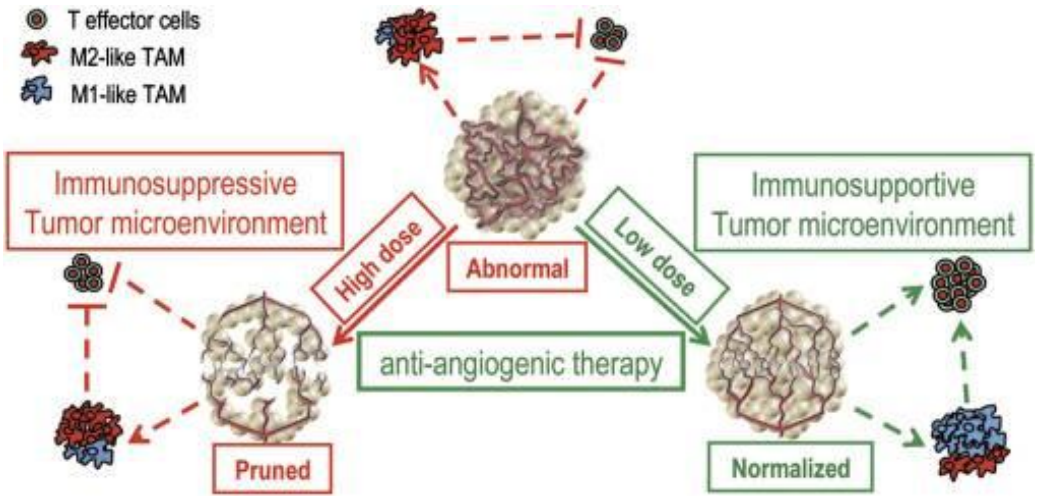
- Anti-PD1 MK-3475 has demonstrated response in Kidney Cancer

- Bevacizumab has been approved for treatment of Kidney Cancer.

Topalian SL, Hodi FS, Brahmer JR, et al: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443-54, 2012

Background

- Lower doses of an anti-VEGF receptor 2 (VEGFR2) antibody treatment enhanced the anti-cancer efficacy of a vaccine therapy in a model of immune tolerant breast CA
  - Demonstrated improvement in tumor vascularization
  - Polarized tumor associated macrophages from an immunosuppressive (M2-like) to an immune-stimulatory (M1-like) phenotype
  - Which facilitated recruitment of activated CD8 (+) T cells and improved tumor infiltration



Huang Y, Yuan J, Righi E, et al: Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A 109:17561-6, 2012

Background

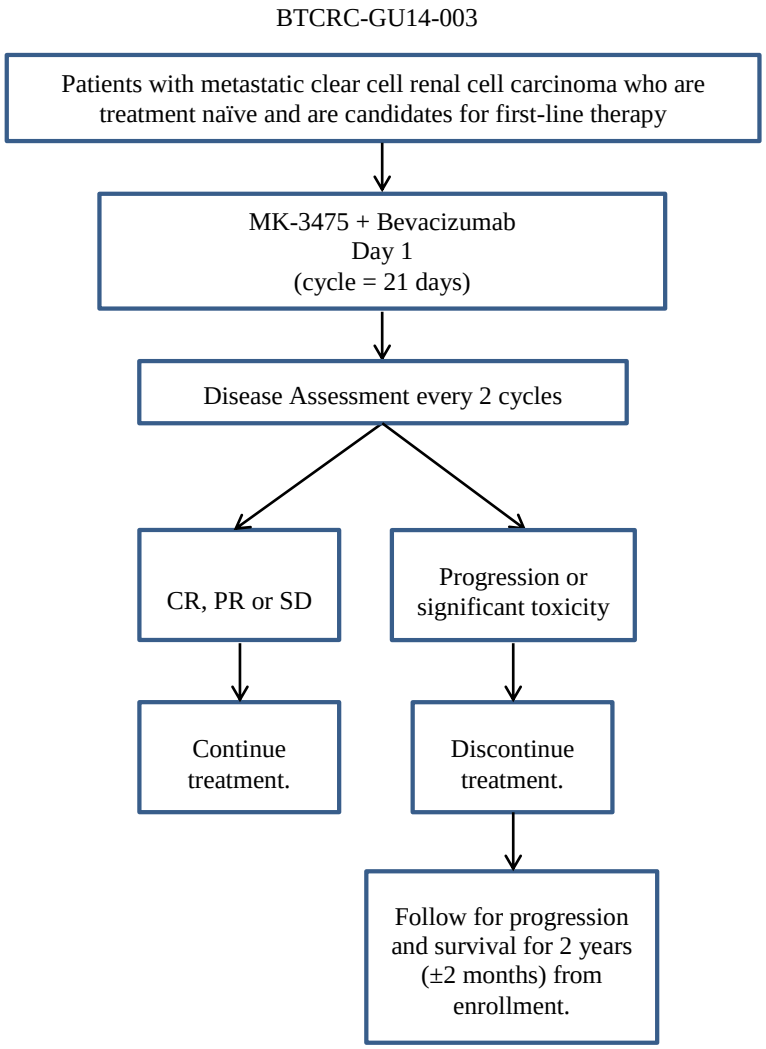
- rh-endostatin, an antiangiogenic, improved the anti-cancer effect of adoptive Cytokine-induced killer (CIK) cells against lung carcinoma.
  - The proposed mechanism was a synergistic therapeutic effect in which endostatin contributed to structural normalization of tumor vasculature
  - Endostatin augmented homing of the CIK cells and subsequently intratumoral CD3(+) T lymphocytes
  - Addition of an anti-angiogenic agent normalized vasculature, reduced hypoxia, and altered the tumor microenvironment to enhance tumor infiltration by transferred CIK cells and T-lymphocytes

Shi S, Wang R, Chen Y, et al: Combining antiangiogenic therapy with adoptive cell immunotherapy exerts better antitumor effects in non-small cell lung cancer models. PLoS One 8:e65757, 2013

Hypothesis

- Dudek et al. hypothesize that through the strategy of adding the anti-VEGF agent bevacizumab to the anti-PD1 agent (MK-3475) we will enhance tumor infiltration by T-lymphocytes, enhancing the clinical activity of PD-1 in renal cell cancer

Phase II SCHEMA



Phase II Objectives

Primary Objective:

- Determine the activity of the combination of MK-3475 and bevacizumab as a first line therapy for subjects with treatment naïve metastatic clear cell RCC as assessed by response rates (complete or partial response) (RR) based on RECIST 1.1.

Secondary Objectives:

- Characterize AE's of MK-3475 in combination with bevacizumab in subjects with treatment-naïve metastatic RCC.
- Evaluate clinical benefit RR (complete, partial response, or stable disease) of MK-3475 in combination with bevacizumab in subjects with treatment-naïve metastatic RCC.
- Measure PFS using RECIST 1.1 at 6 months in subjects with treatment-naïve metastatic RCC treated with MK-3475 in combination with bevacizumab.
- Measure OS at 2 years in subjects with treatment-naïve metastatic RCC treated with MK-3475 in combination with bevacizumab.

Correlatives

- Evaluate PD-L1 expression of archived tumor tissue and correlate to clinical response
- Assess tumor vascular density of archived tumor tissue and correlate to clinical response.
- Assess CD4(+) and CD8(+) T-cell infiltration of archived tumor tissue and correlate to clinical response.
- Assess number of circulating cancer cells at baseline and during treatment and correlate to clinical response
- Measure soluble PD-L1 level at baseline and during treatment and correlate to clinical response.
- Measure VEGFc at baseline and during treatment and correlate to clinical response.
- Samples for future studies

Prostate Cancer

Therapeutic Cancer Vaccines

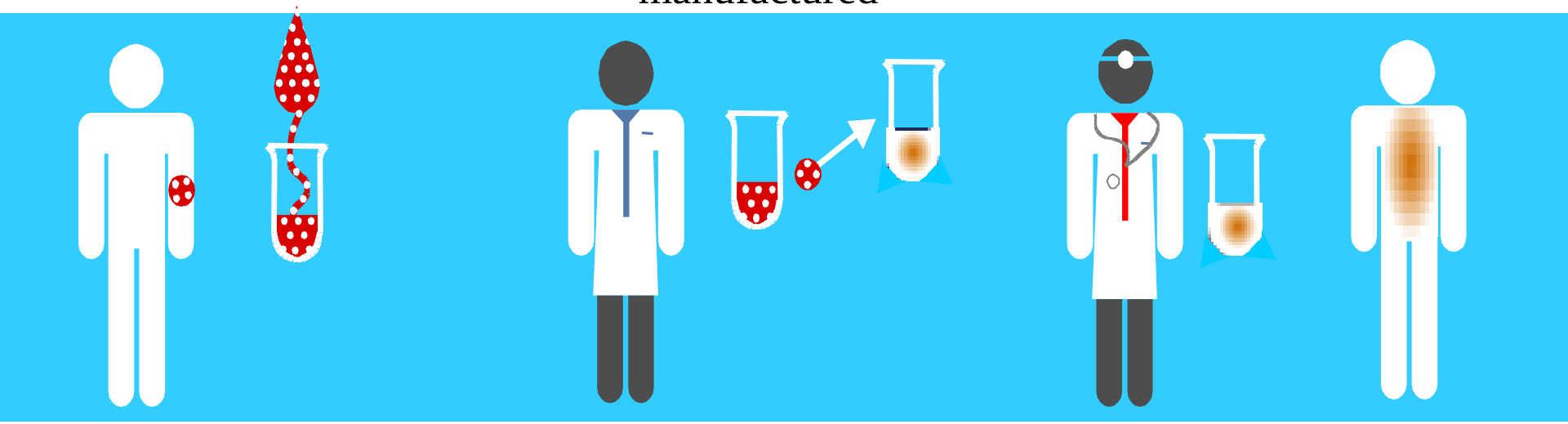
- Designed to generate a targeted anti-tumor immune response
- Associated with minimal toxicities
- May have delayed effects relative to standard cytotoxic therapies
- May have impact beyond the period of administration

Sipuleucel-T

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is
manufactured

Day 3-4
Patient is infused



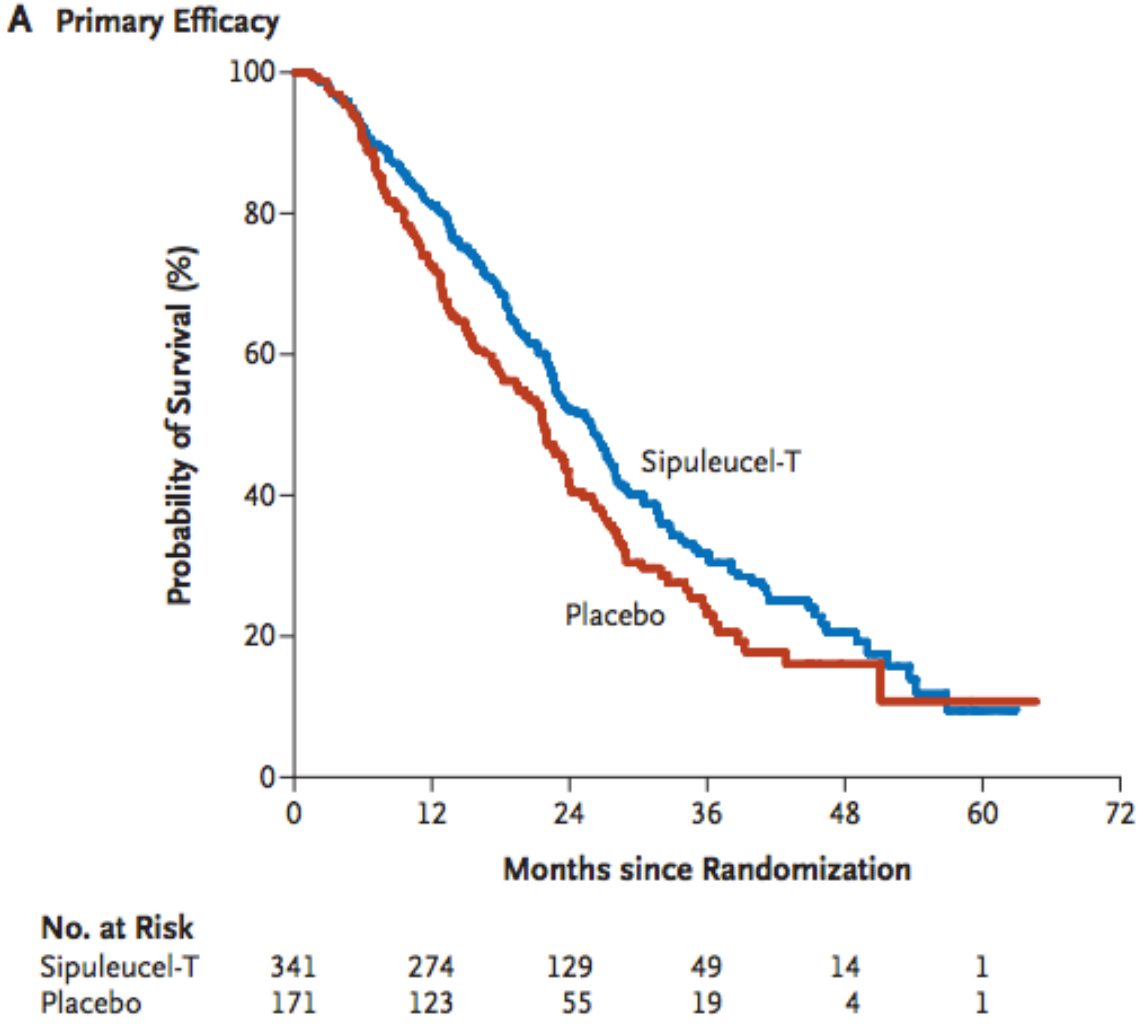
Apheresis Center

Company

Doctor's Office

Sipuleucel-T

First Cancer Vaccine Approved by the US FDA

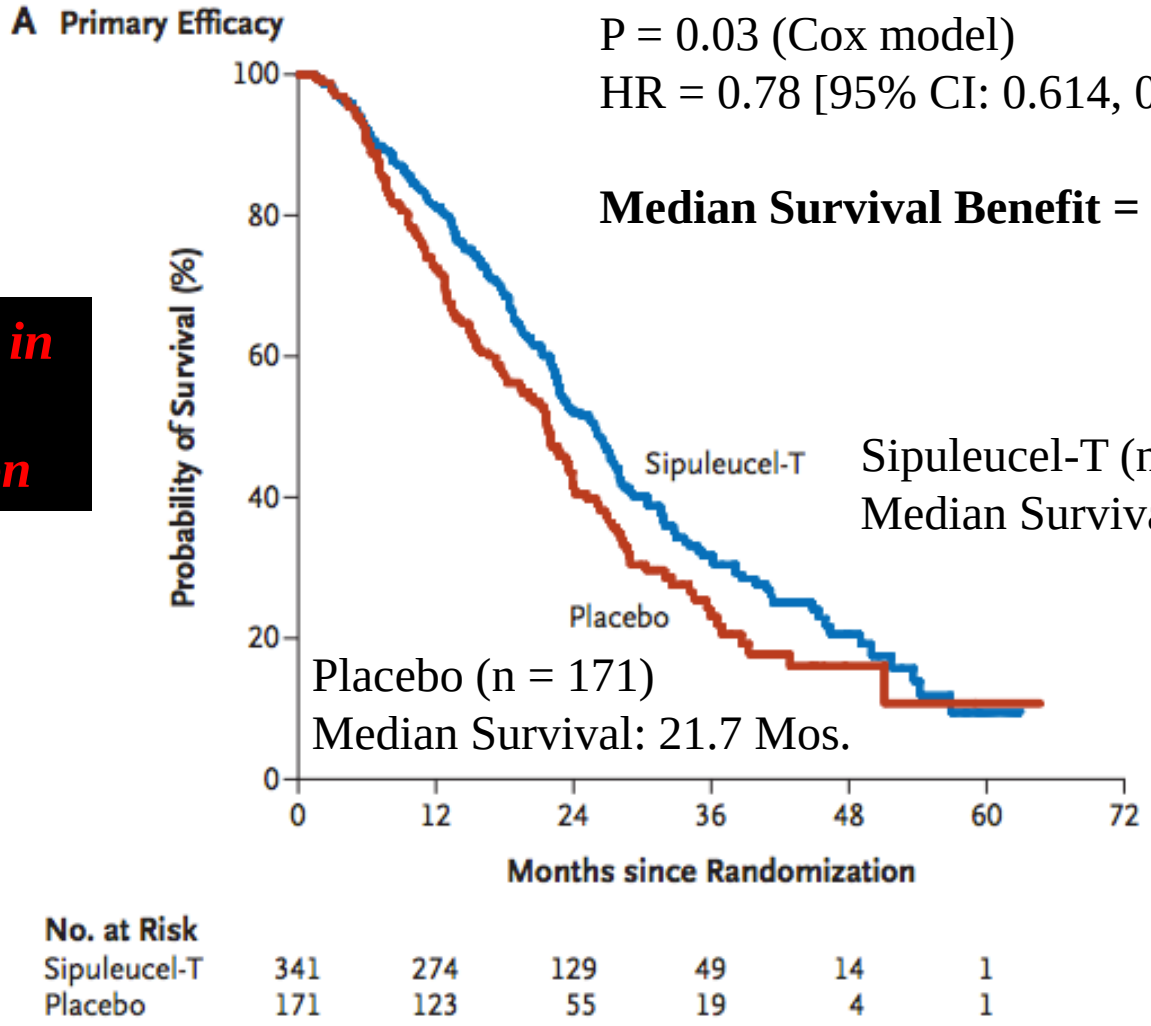


Kantoff et al. NEJM 2010

Sipuleucel-T

First Cancer Vaccine Approved by the US FDA

No Change in Time to Progression



P = 0.03 (Cox model)
HR = 0.78 [95% CI: 0.614, 0.979]

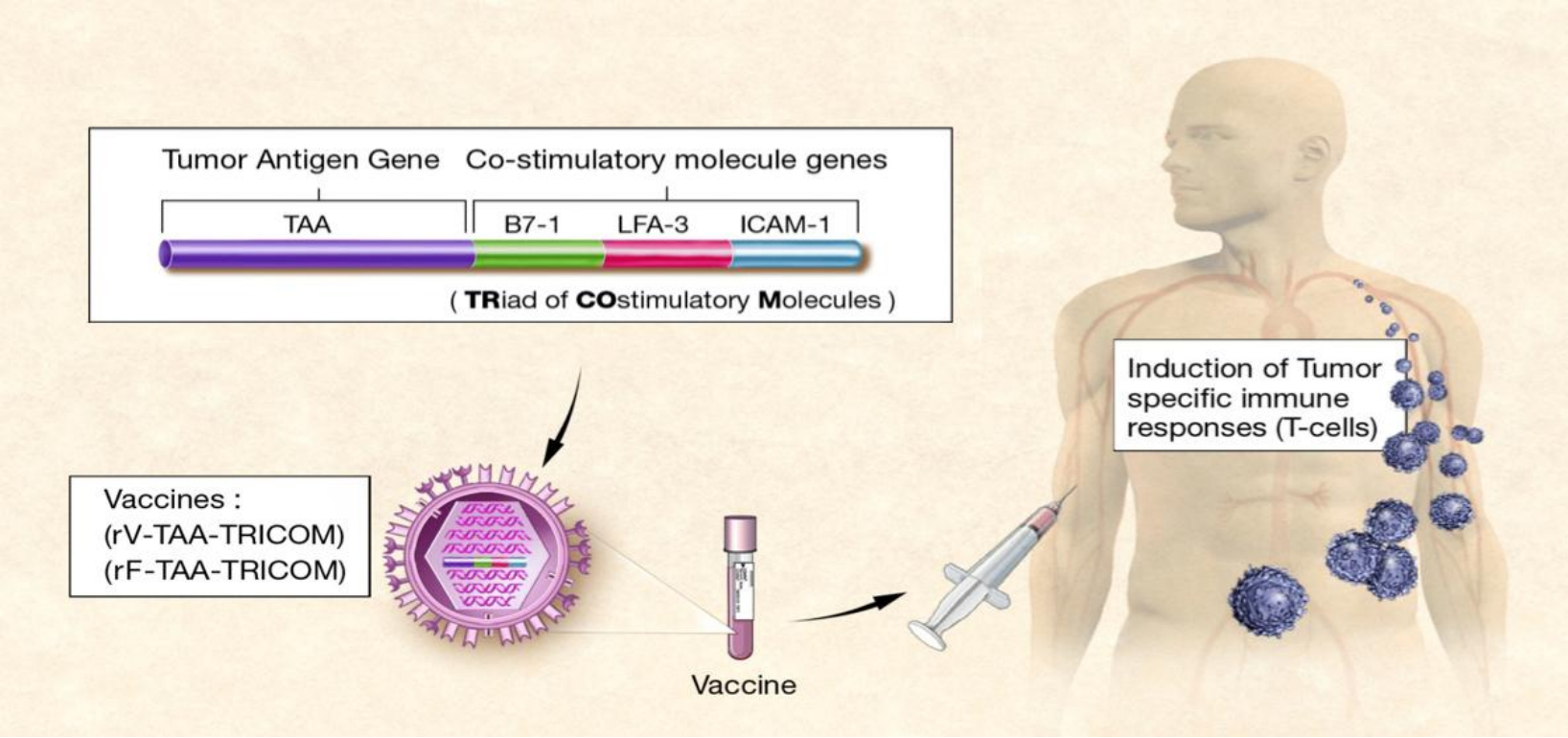
Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

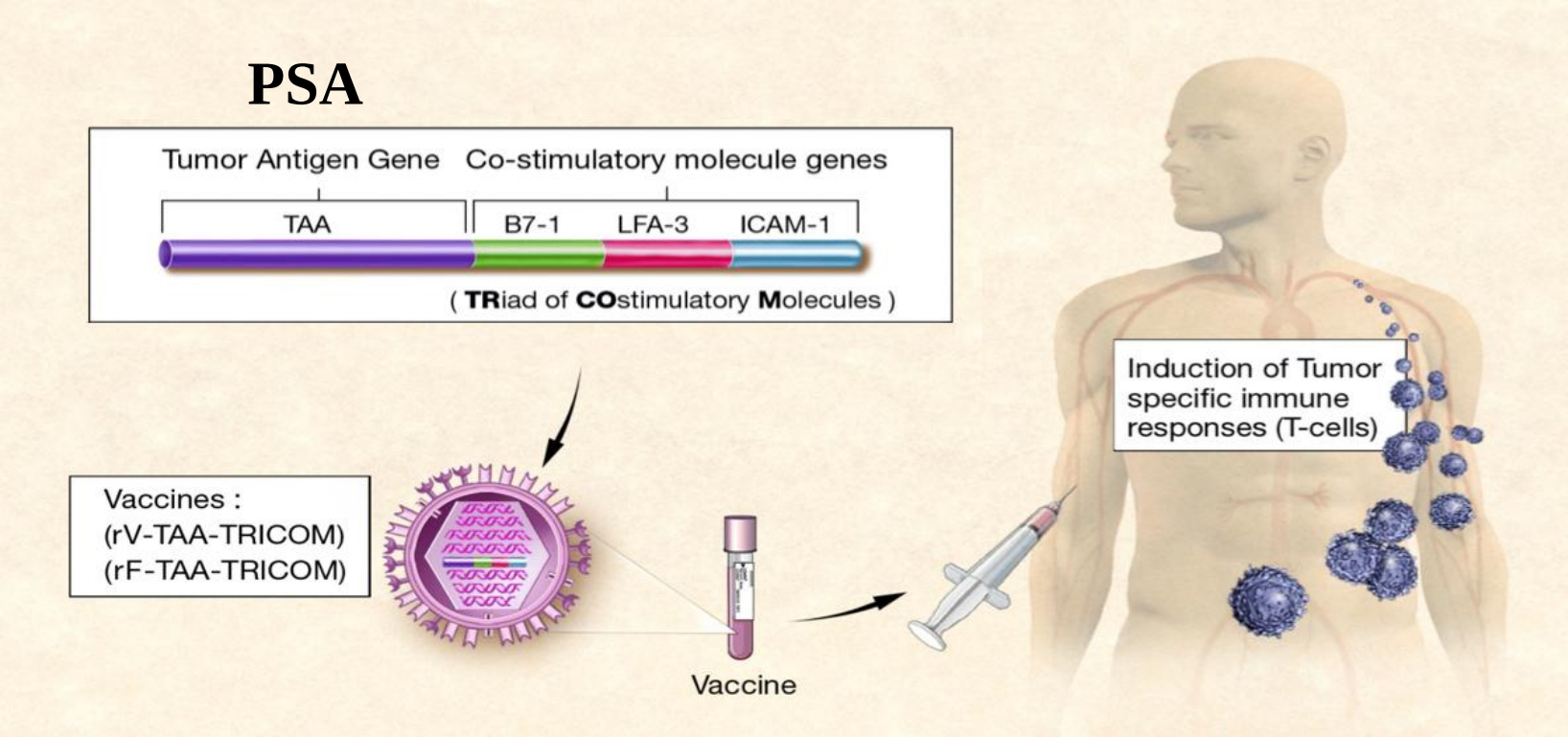
Placebo (n = 171)
Median Survival: 21.7 Mos.

Kantoff et al. NEJM 2010

Pox Viral-Based Vaccines

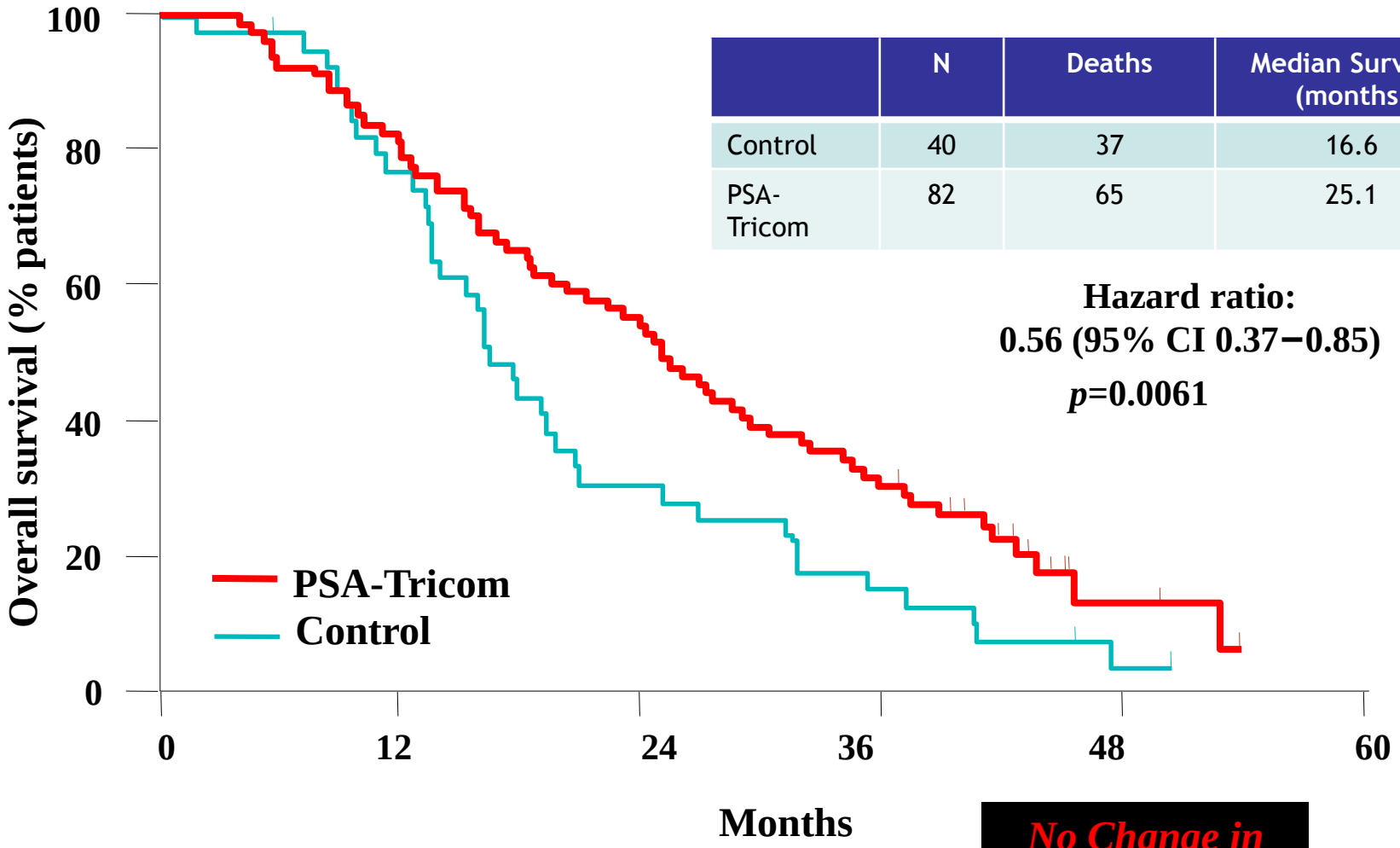


Pox Viral-Based Vaccines



PSA-Tricom "Off the Shelf"

PSA-TRICOM Significantly Extended Overall Survival



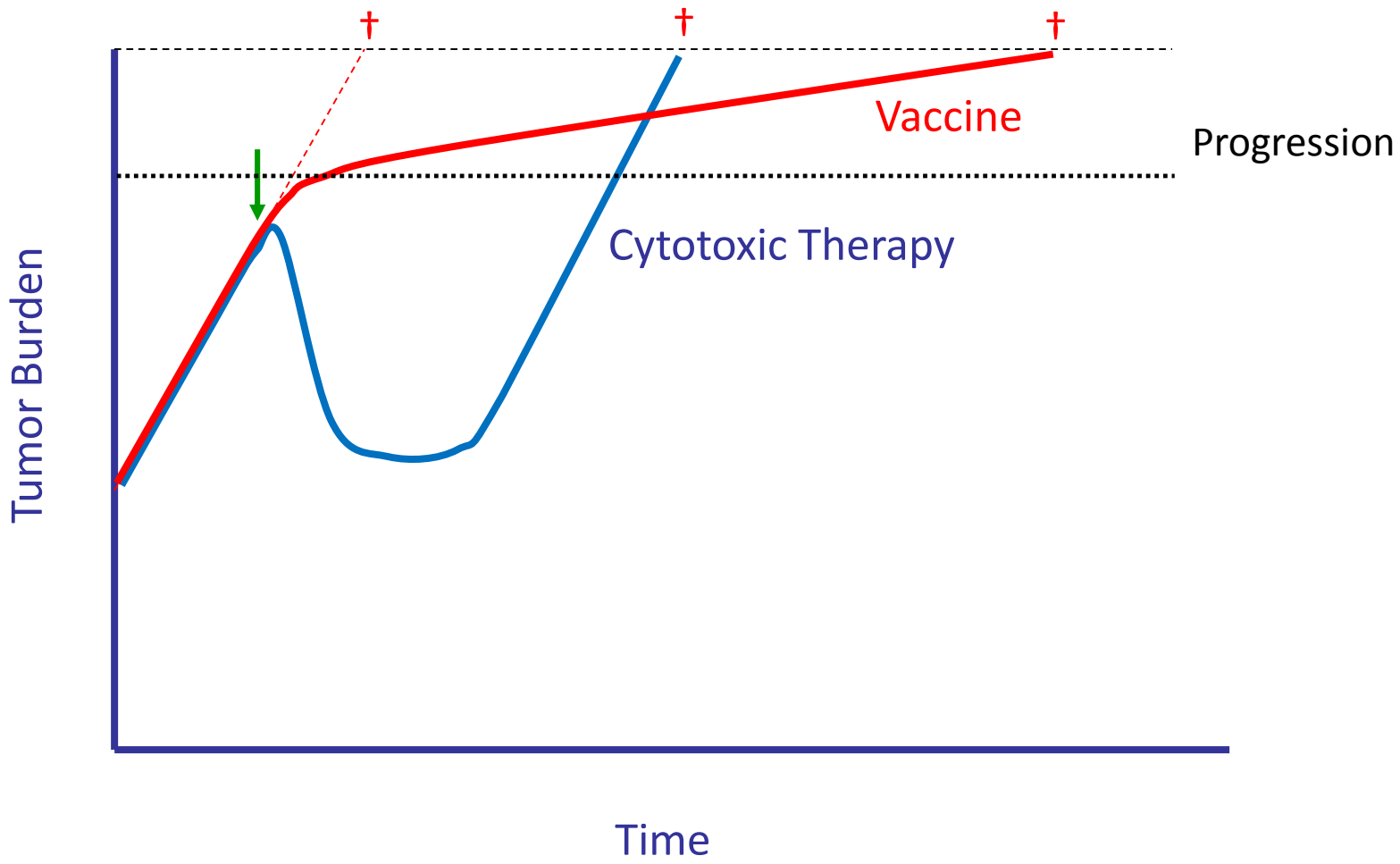
	N	Deaths	Median Survival (months)
Control	40	37	16.6
PSA-Tricom	82	65	25.1

Hazard ratio:
0.56 (95% CI 0.37−0.85)
***p*=0.0061**

No Change in Time to Progression

Kantoff PW, et al. J Clin Oncol. 2010

How can vaccines improve survival without impacting time to progression?



Stein WD, Clin Cancer Res, 2010
Madan RA, Semin Oncol, 2012

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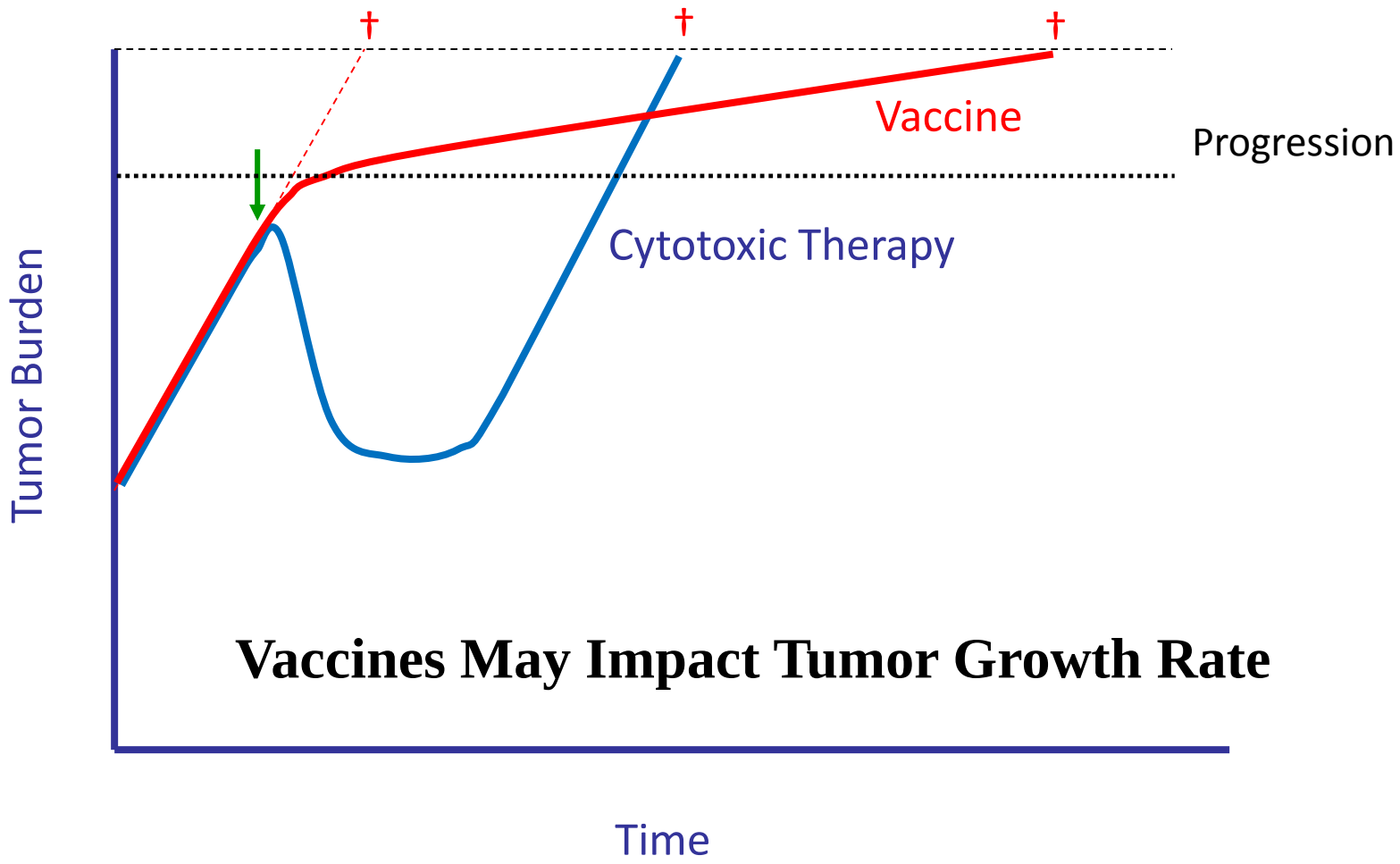
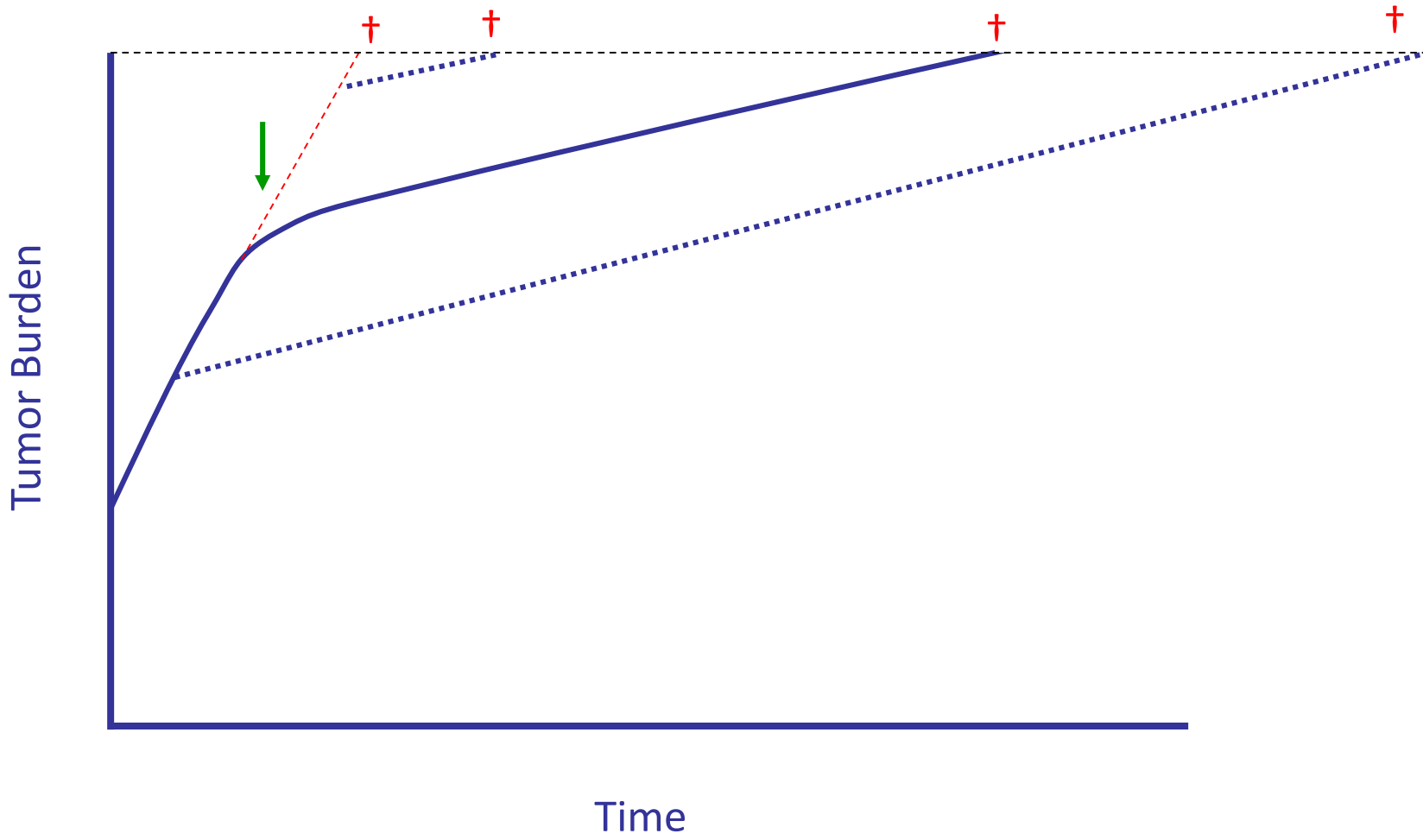


Stein WD, Clin Cancer Res, 2010
Madan RA, Semin Oncol, 2012

Earlier Vaccine Use May Have Greater Impact on Clinical Outcomes



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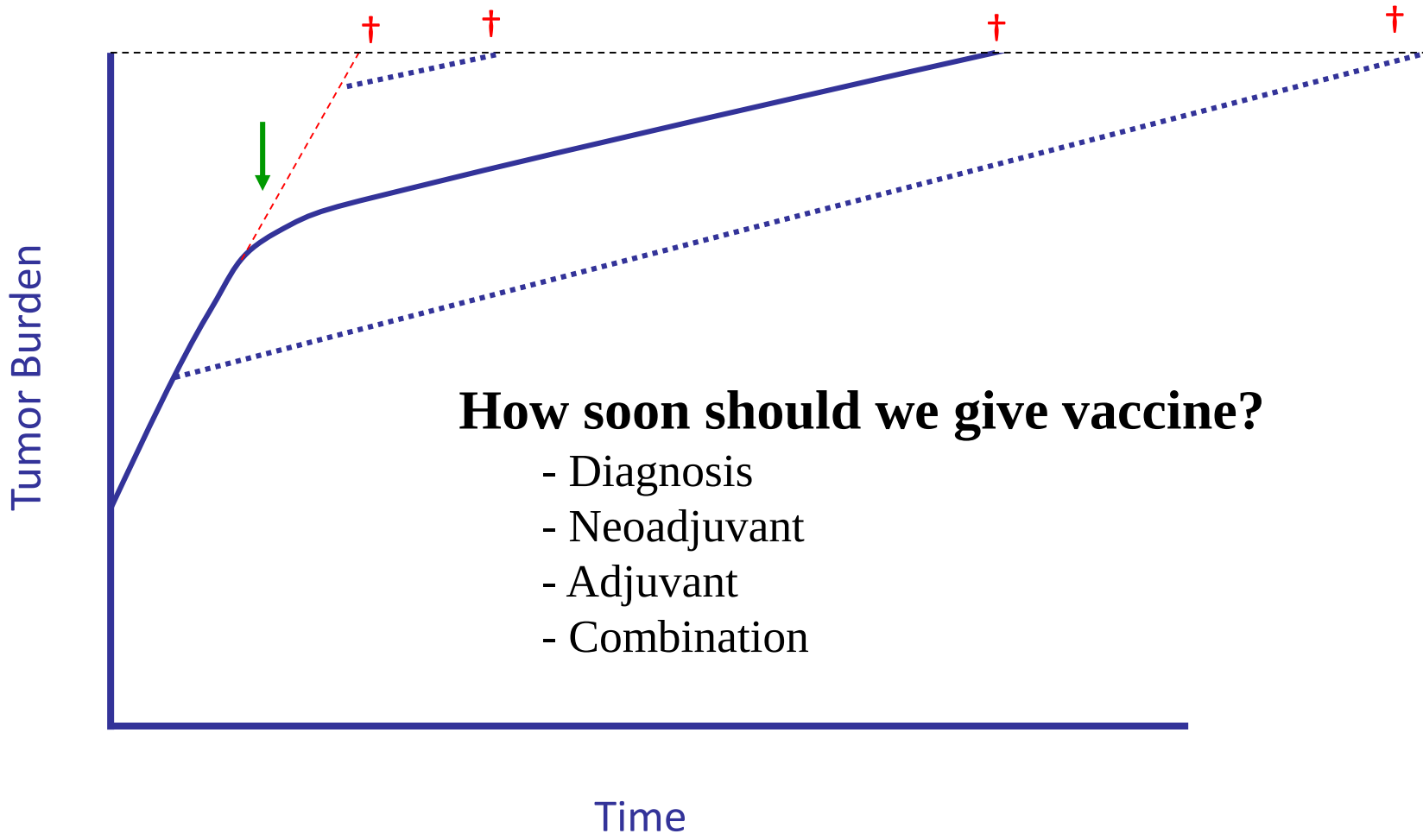
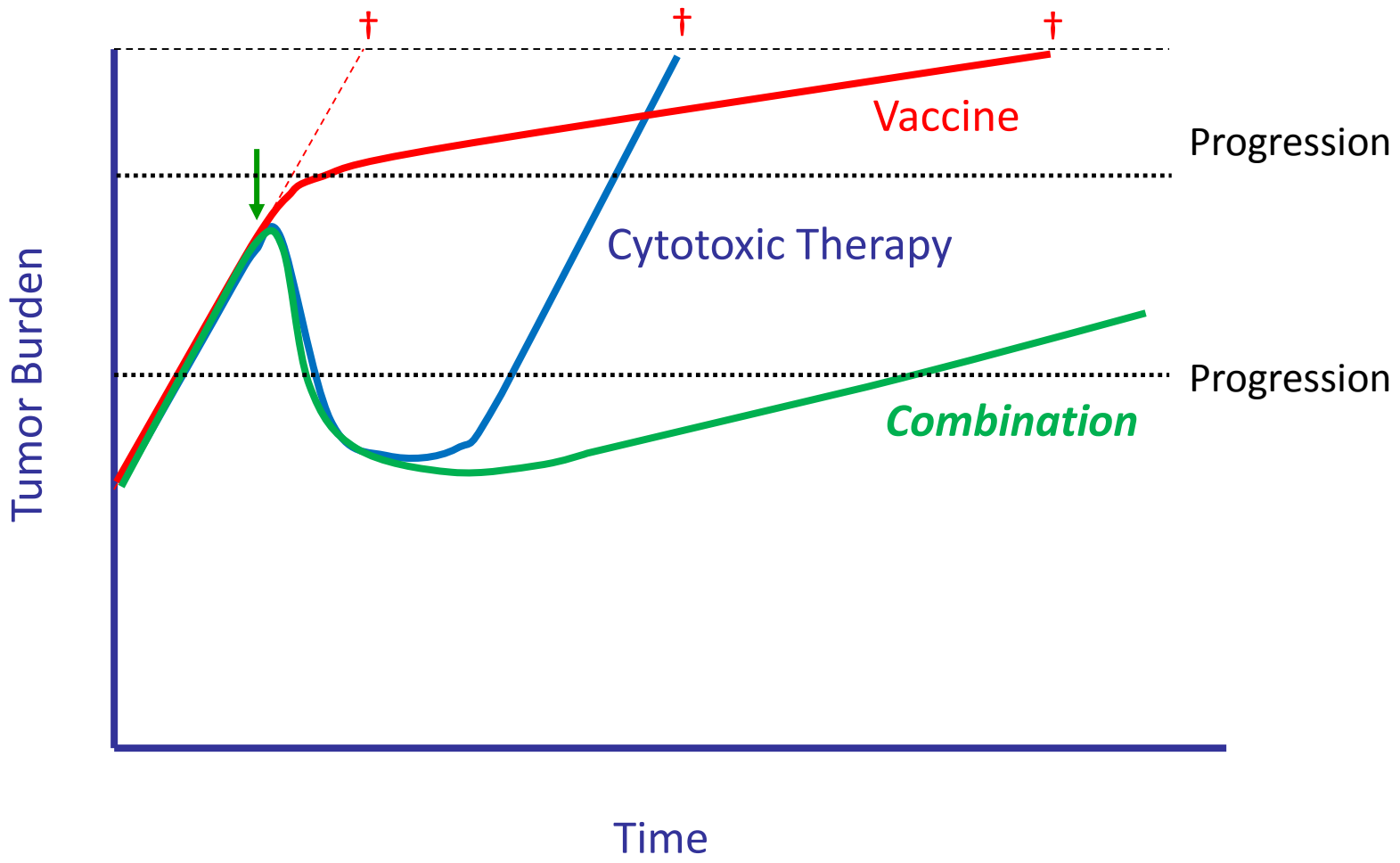
Earlier Vaccine Use May Have Greater Impact on Clinical Outcomes



Stein WD, Clin Cancer Res, 2010
Madan RA, Semin Oncol, 2012

Vaccines in *Combination* with Other Therapies May Improve Time To Progression



Stein WD, Clin Cancer Res, 2010
Madan RA, Semin Oncol, 2012

Bladder Cancer

Bladder Cancer

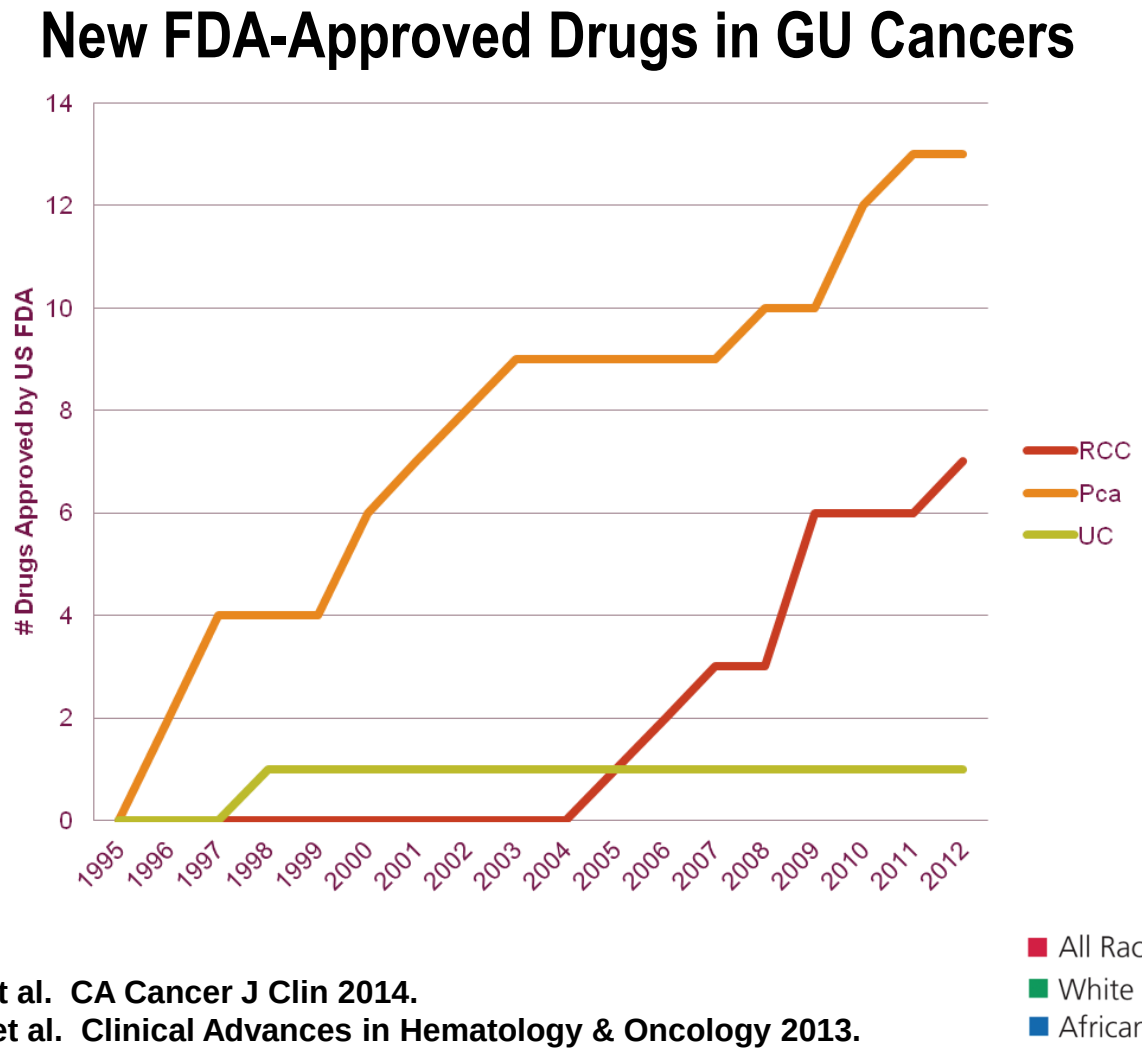
- Incidence:
  - 4th most common cancer in men
  - 12th most common cancer in women
  - 74,000 new cases and 16,000 deaths in 2015 alone

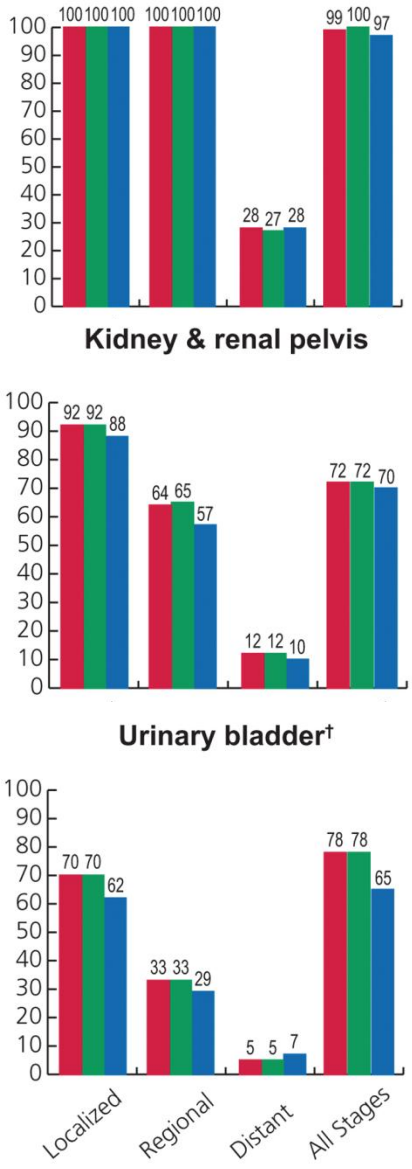
- Represents 7% of all cancers and 3% of all cancer deaths

- Recurrence and routine surveillance/treatment make bladder cancer ***most expensive malignancy to treat*** from diagnosis to death ($187,241/patient in 2001)

Siegel et al. CA Cancer J Clin 2015.
Botteman et al. Pharmacoeconomics 2003.

No Therapeutic Advance in Last Two Decades
5-Yr Survival Rates Poor in Advanced Disease





Siegel et al. CA Cancer J Clin 2014.
Galsky et al. Clinical Advances in Hematology & Oncology 2013.

No Therapeutic Advance in Last Two Decades
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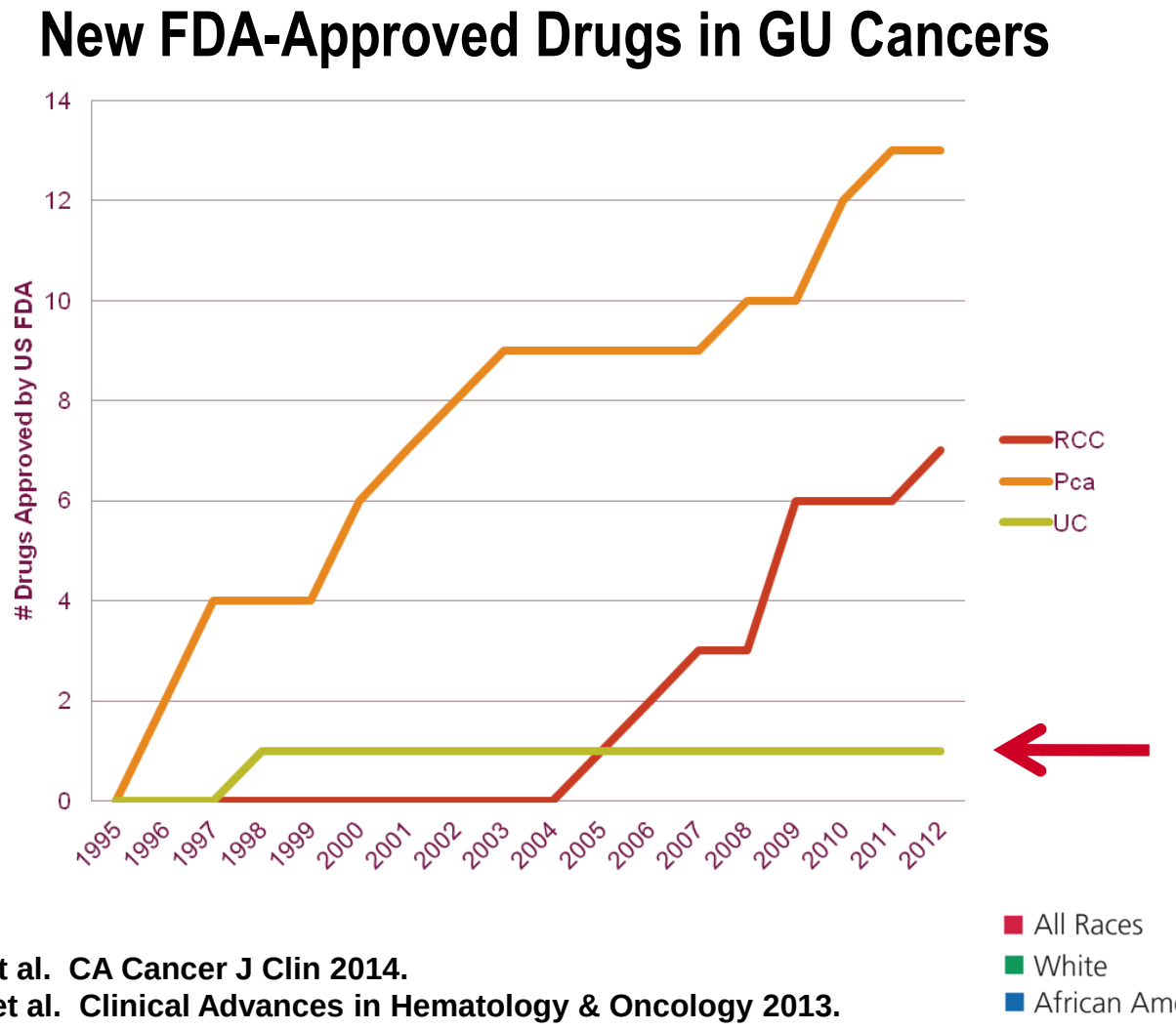
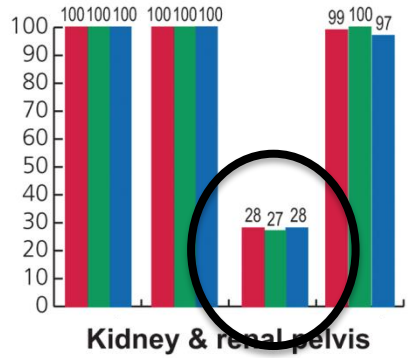
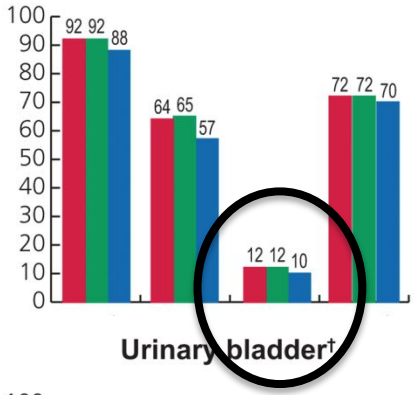
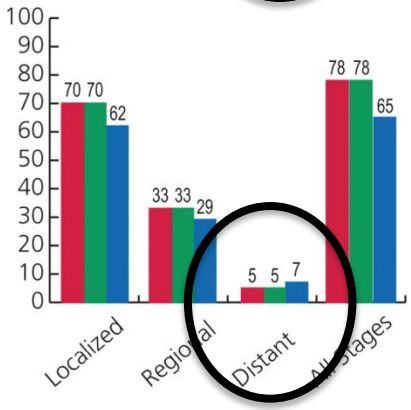








Siegel et al. CA Cancer J Clin 2014.
Galsky et al. Clinical Advances in Hematology & Oncology 2013.

PANVAC PROTOCOL

Rationale and Background

- HG NMIBC (Ta, T1, and/or CIS) is managed by BCG but still with ~35% initial failure rate after induction course in terms of progression and/or recurrence.

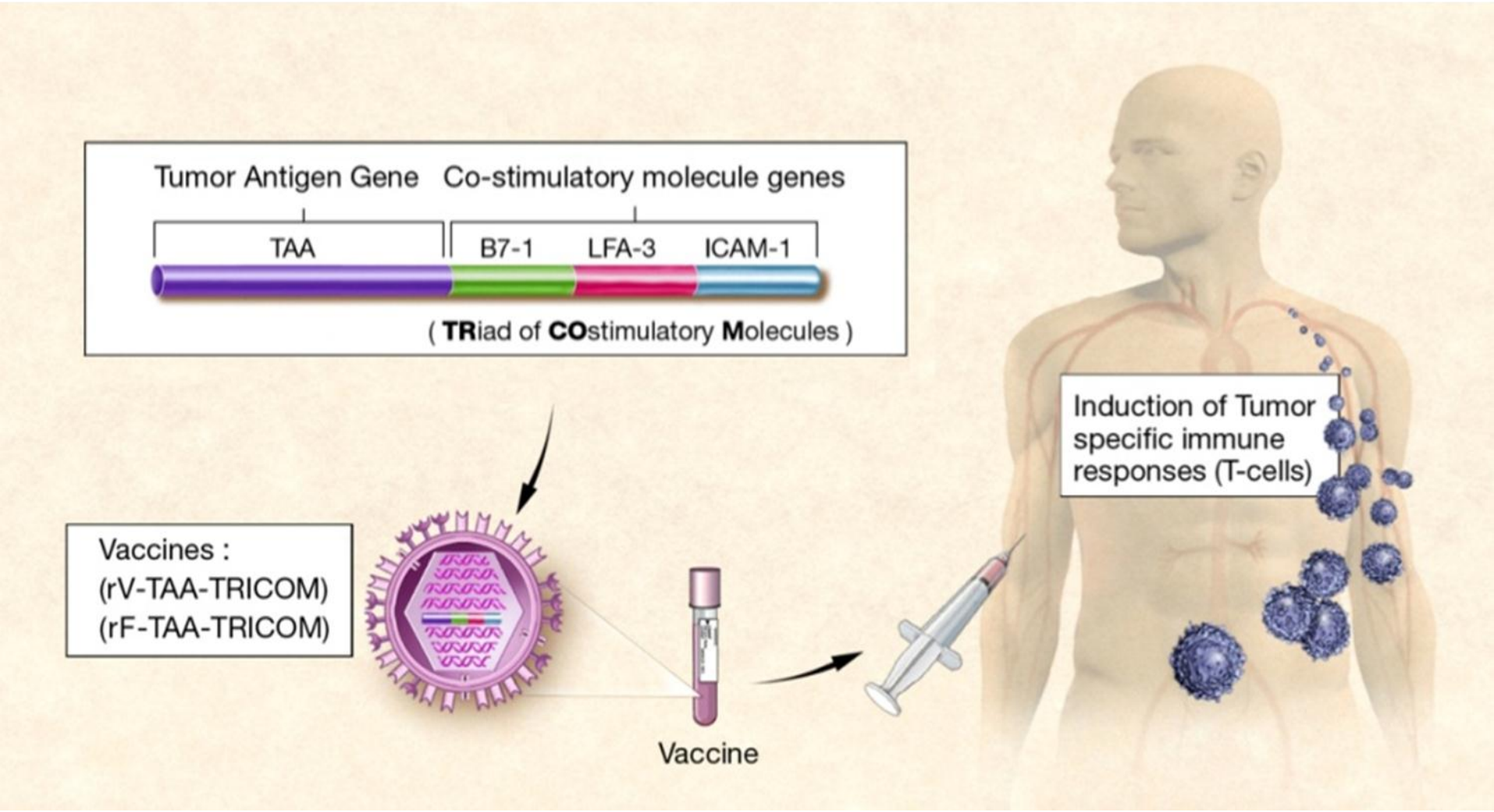
- Although 20-35% of cases that fail an initial course can benefit from a second induction course, patients best served by radical cystectomy if continue to fail to respond.

- Radical cystectomy is potentially morbid and so **unmet clinical need** for patients that still have NMIBC that fails to respond to BCG.

Rationale and Background

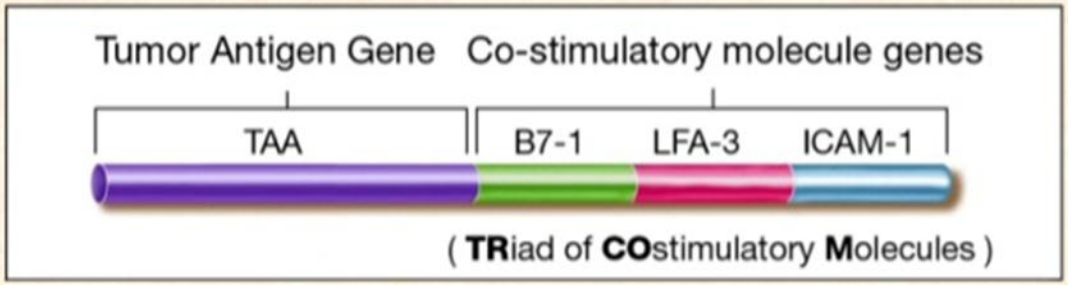
- BCG works by unclear immunologic mechanism:
  - Athymic animals only respond to BCG when T cells administered
  - BCG-induced macrophage cytotoxicity important and promoted by Th1 immune system (TNF-a, IFN-y, IL-12, IL-18) and inhibited by Th2 immune system (IL-4, IL-10) and Tregs
  - T cell infiltration important as degree of infiltration (CD3, CD4, and CD8) with immune cells is greater in patients with a complete response to BCG

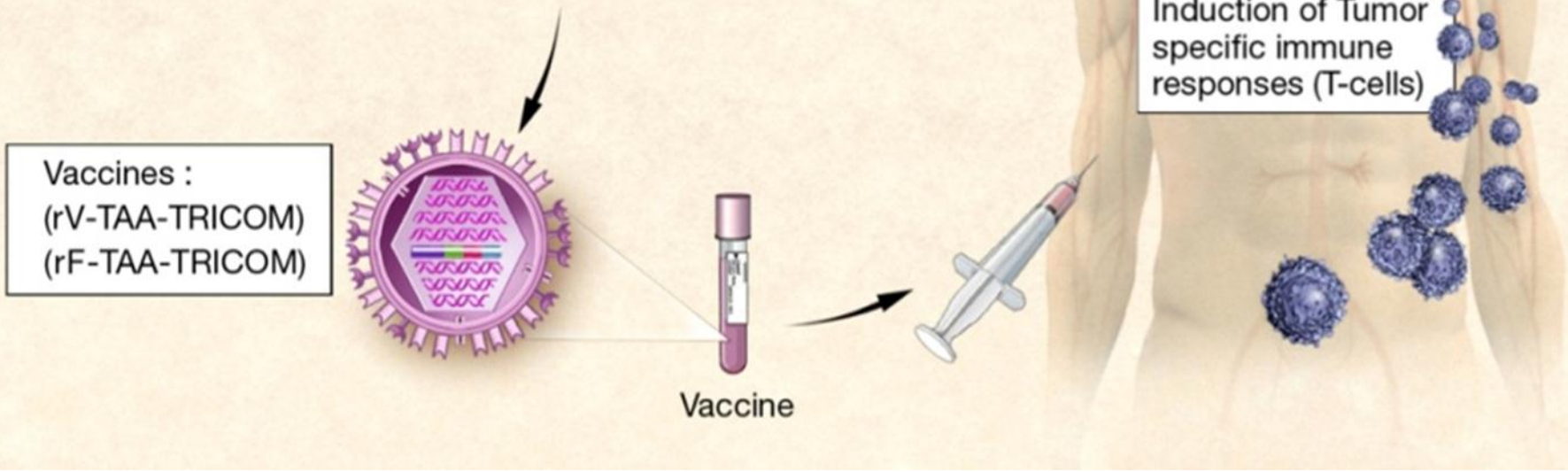
Pox Vector Vaccine: PANVAC



Pox Vector Vaccine: PANVAC

CEA, MUC-1





Rationale for PANVAC

- Pox viral vector-based vaccine than can induce CD4 and CD8 antigen-specific immune response against *MUC-1* and *CEA*
  - Also contains 3 co-stimulatory molecules (Tri-Com)
  - Excellent safety record in other tumors
  - Administered subcutaneously

- **MUC-1** expression in up to 93% bladder tumors

- **CEA** expressed in 76% of HG tumors and 59% of T1 bladder tumors

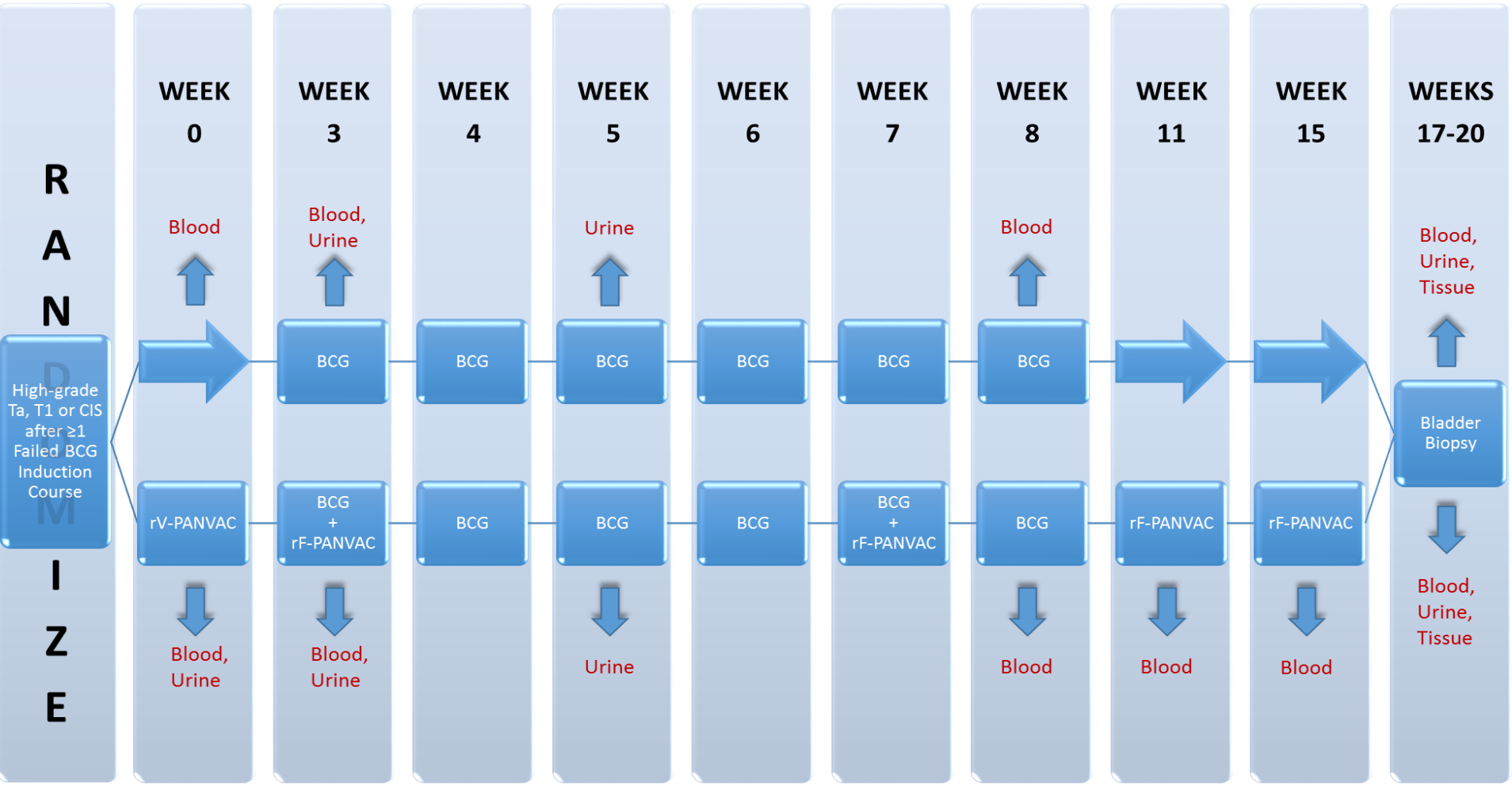
- Postulate that this drug may enhance an immune response in HG tumors that have not responded to BCG

Hypotheses/Objectives

- Primary:
  - PANVAC will augment BCG-induced cytotoxic T lymphocyte response against bladder cancer cells expressing MUC-1 and/or CEA when given with BCG and will result in greater **12 month RFS** than BCG alone in patients who failed to respond to at least 1 previous induction course of BCG

- Secondary:
  - PANVAC+BCG will have greater **PFS** and greater **immune response** than BCG alone

Schema


RANDOMIZE
High-grade Ta, T1 or CIS after ≥1 Failed BCG Induction Course
WEEK 0
WEEK 3
WEEK 4
WEEK 5
WEEK 6
WEEK 7
WEEK 8
WEEK 11
WEEK 15
WEEKS 17-20
Blood
Blood, Urine
Urine
Blood
Blood, Urine, Tissue
BCG
rV-PANVAC
BCG + rF-PANVAC
rF-PANVAC
Bladder Biopsy
Blood, Urine
Urine
Blood
Blood, Urine, Tissue

Eligibility

- Adults with histologically confirmed high grade (Ta, T1, and/or CIS) UC of bladder who “failed” at least one induction course of BCG (either progressed and/or recurred)

- Patients who fail ≥1 induction course of BCG have been offered radical cystectomy and either refuse or are not surgical candidates for cystectomy

- ECOG PS 0-2

Immune Correlates

- Biopsy (compared day 0 and week 17 tissue) IHC for:
  - CEA and MUC-1
  - CD4, CD8, and Tregs (by DS for Foxp3 and CD4)
  - Myeloid derived suppressor cells (MDSC)
- PBMCs and sera at 4 time points (week 0 (prior to vaccination), week 3 (prior to BCG), week 8 (prior to last BCG), and week 17 (end of treatment):
  - Flow cytometry for 23 markers (e.g. CD4, CD8, Tregs, MDSCs, and NK)
  - In HLA-A2 allele patients, ELISPOT for CD8 T-cell responses for CEA and MUC-1 and cascade antigen Brachyury
  - If sufficient sample available, CD4 specific responses to CEA will be measured
  - Study sera for Ab to CEA
- Urine
  - Check levels of urinary cytokines at week 3 and week 5 to assess cytokine production in response to BCG and PANVAC therapy
- PPD
  - See if any correlation with immunologic response

Conclusions

- Immunotherapy continues to be an area of active investigation for GU malignancies
- Multimodal therapy is most likely to provide the greatest benefit to the largest number of patients
- Clinicians will need to become comfortable with new types of therapies and the management of their toxicities
- **Referral to/participation in clinical trials remains critical**

Acknowledgements

- James Gully, MD, PhD (NCI)
- Ravi Madan, MD (NCI)
- Piyush Agarwal, MD (NCI)
- Arkadiusz Dudek, MD, PhD (UIC)

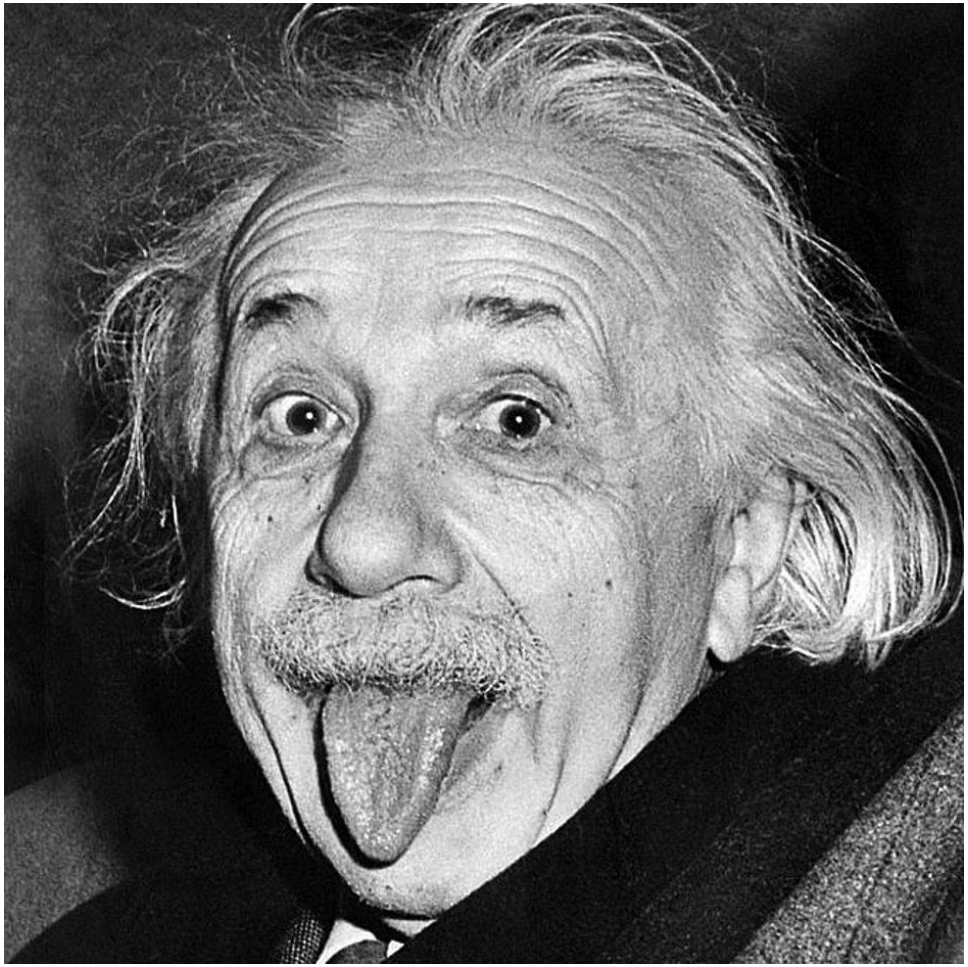
Future Directions

- CINJ Clinical Trials:

  http://cinj.org/clinical-trials/index

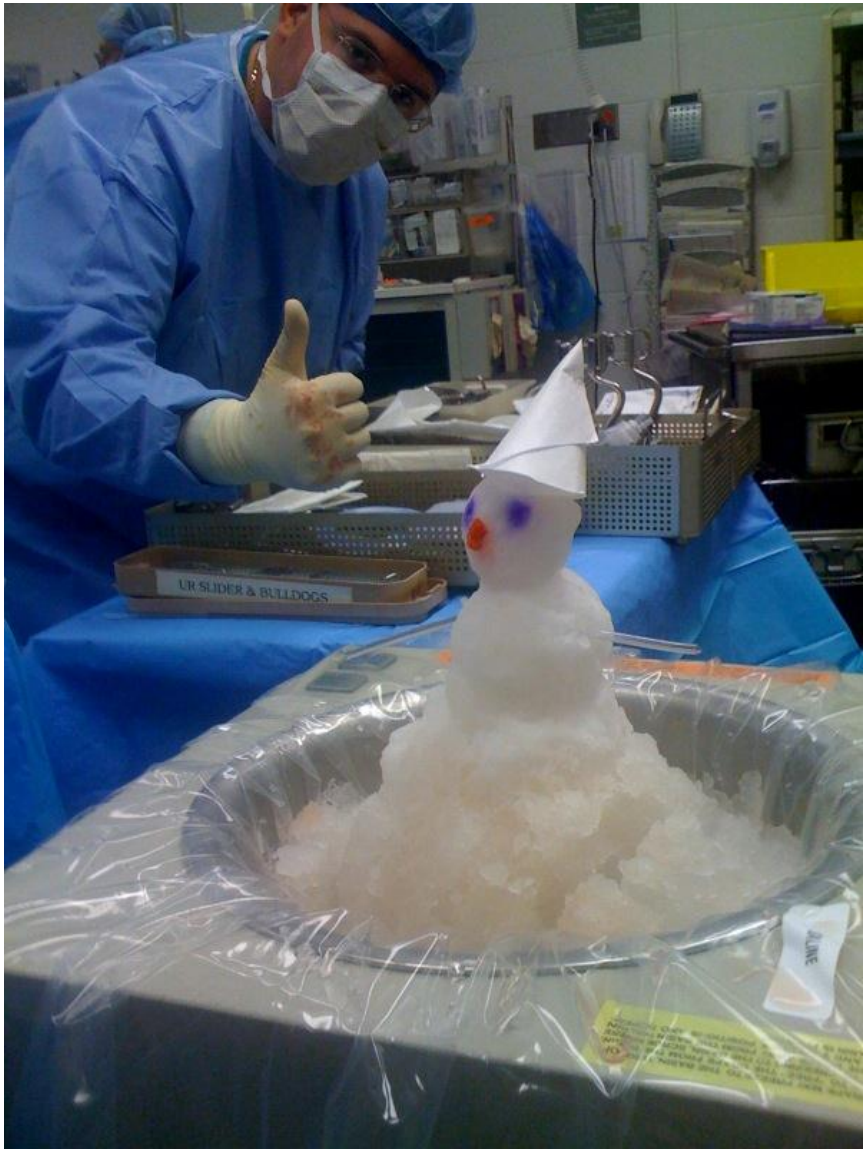
  http://cinj.org/

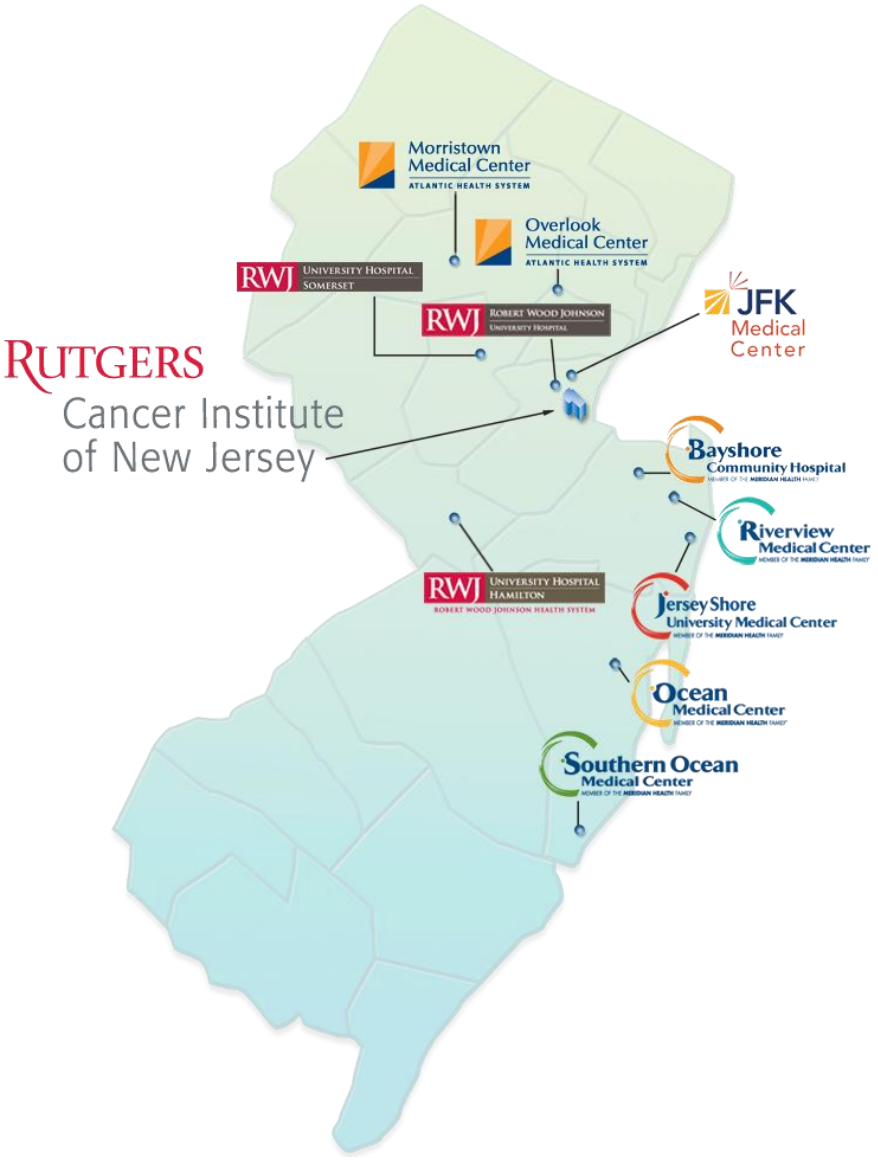
Questions?



"If we knew what we were doing it wouldn't be research."

Thank You!


UR SLIDER & BULLDOGS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